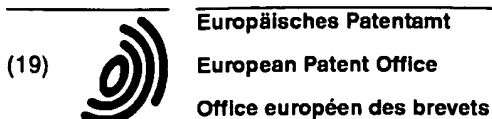


USSN: 10/676,956 Filed: 9/30/2004
 Applicant: C.D. ROBERTS et al.
 Docket: 355491-1250 Ref No: F1



(11) **EP 1 117 669 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention
 of the grant of the patent:
29.01.2003 Bulletin 2003/05

(51) Int Cl.7: **C07F 9/6561, A61K 31/675**

(86) International application number:
PCT/GB99/03207

(21) Application number: **99949151.7**

(87) International publication number:
WO 00/018775 (06.04.2000 Gazette 2000/14)

(22) Date of filing: **27.09.1999**

(54) **ANTIVIRAL PURINE DERIVATIVES**
ANTIVIRALE PURIN-DERIVATE
DERIVES DE PURINE ANTIVIRAUX

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE
 Designated Extension States:
SI

(72) Inventors:
 • **MCGUIGAN, Christopher**
Whitchurch Cardiff CF4 2EH (GB)
 • **BALZARINI, Jan**
B-3001 Heverlee (BE)

(30) Priority: **28.09.1998 GB 9821058**

(74) Representative: **Howard, Paul Nicholas et al**
Carpmaels & Ransford
43 Bloomsbury Square
London WC1A 2RA (GB)

(43) Date of publication of application:
25.07.2001 Bulletin 2001/30

(73) Proprietors:
 • **UNIVERSITY COLLEGE CARDIFF**
CONSULTANTS LTD.
Cardiff CF1 3XR (GB)
 • **REGA FOUNDATION**
3000 Leuven (BE)

(56) References cited:
EP-A- 0 369 409 **EP-A- 0 434 450**
EP-A- 0 468 866 **WO-A-92/06102**
WO-A-96/29336

EP 1 117 669 B1

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 1 117 669 B1

Description

[0001] The present invention relates to a chemical compound. In particular the present invention relates to a chemical compound suitable for use as an anti-viral agent. The present invention also relates to the therapeutic use of the present chemical compound, to a pharmaceutical composition containing the present compound and to use of the present compound in the manufacture of a medicament.

[0002] Since the recognition of human acquired immunodeficiency syndrome (AIDS) much interest and research activity has been directed to its understanding and to attempting to provide a means of treatment. The human immunodeficiency virus (HIV) has been identified as the presumed aetiological agent in AIDS. A large literature now exists related to the use of a wide variety of chemical compounds having as their object a demonstration of anti-viral activity with respect to HIV, hepatitis B virus (HBV), herpes and other viruses.

[0003] A class of compounds which has demonstrated anti-viral activity and which has been the subject of a large amount of research are nucleoside analogues.

[0004] An example of such a compound is "Abacavir" which is a substituted adenine analogue (Foster R.H. & Faulds D. Drugs 1998 55 729-736). This compound has entered clinical use due to the potential activity and stability of the compound displayed in preliminary work.

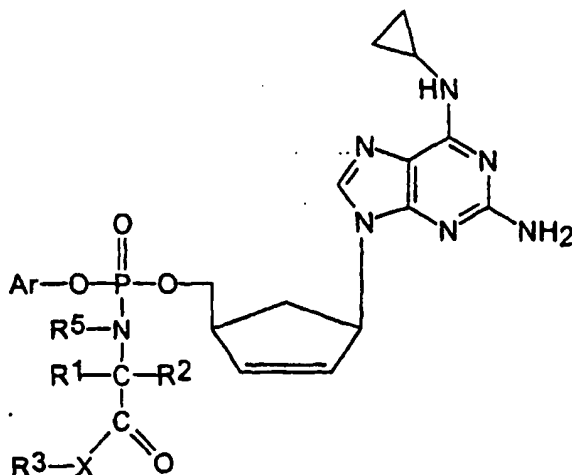
[0005] WO-9629336 relates to a class of nucleoside analogues said to be highly active with respect to HIV. In particular WO-9629336 addresses the problem of providing compounds which are said to be highly potent *in vitro* viral inhibitors in both TK⁻ and TK⁺ cells. The compounds disclosed in WO-9629336 are phosphoramidates of purine or pyrimidine nucleoside analogues. Such compounds can however display chemical, for example acid, or biological, for example nucleoside phosphorylase, instability towards glycoside bond cleavage. Consequential deactivation may limit their potential clinical efficacy.

[0006] A compound however to be potentially useful in a clinical setting needs to exhibit a number of other properties as well as demonstrating, at least in *in vitro* tests, a sufficient and desired anti-viral activity. Primarily, these other properties comprise good pharmacokinetic properties, sufficient stability in the compound to permit its ease of handling and supply, and sufficiently low toxicity to permit its administration with an acceptable level of side effects to a patient in need of treatment for the viral infection in question.

[0007] In practice however it is frequently found that attempts to modify a compound demonstrating anti-viral activity *in vitro*, in order to improve its other properties, can have a detrimental effect on the anti-viral activity it displays. Ideally moreover any compound proposed for clinical trials needs also to have a ready means of administration and to be prepareable by an economically viable route.

[0008] It is an object of the present invention to provide a novel class of compounds exhibiting potent anti-viral, in particular anti HIV and/or HBV activity, in combination with good pharmacokinetic and stability properties and exhibiting sufficiently low toxicity so as to provide a compound having beneficial properties for clinical use.

[0009] According to the present invention there is provided a compound according to the following formula (I):



wherein

Ar is an aryl group,

EP 1 117 669 B1

R¹ and R² are independently selected from the group comprising H, alkyl and aryl groups;

X is selected from the group comprising O, NH, NR⁴ and S wherein R⁴ is selected from the group comprising alkyl and aryl groups;

5 R⁵ is selected from the group comprising H, alkyl and aryl groups, wherein when R¹ and R⁵ are each alkyl they may be linked to form a 5- or 6- membered ring;

and R³ is selected from the group comprising H, alkyl, aryl, heterocyclic and polycyclic groups, or a pharmaceutically acceptable derivative or metabolite thereof.

[0010] The present invention includes salts and physiologically functional derivatives of the presently defined compounds.

10 [0011] Reference in the present specification to an alkyl group means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic, the alkyl group is preferably C₃ to C₁₂, more preferably C₅ to C₁₀, more preferably C₅ to C₇. Where acyclic, the alkyl group is preferably C₁ to C₁₆, more preferably C₁ to C₆, more preferably methyl or ethyl.

15 [0012] Reference in the present specification to an aryl group means an aromatic group, such as phenyl or naphthyl, or a heteroaromatic group containing one or more, preferably one, heteroatom for example O, N and/or S, such as pyridyl, pyrrolyl, furanyl and thiophenyl. Preferably, the aryl group comprises phenyl or substituted phenyl.

[0013] The alkyl and aryl groups may be substituted or unsubstituted, preferably unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent. Substituents may include halogen atoms and halomethyl groups such as CF₃ and CCl₃; oxygen containing groups such as oxo, hydroxy, carboxy, carboxyalkyl, alkoxy, alkoyl, alkoxyl, aryloxy, aryloyl and aryloxy; nitrogen containing groups such as amino, alkylamino, di-alkylamino, cyano, azide and nitro; sulphur containing groups such as thiol, alkylthiol, sulphonyl and sulfoxide, heterocyclic groups which may themselves be substituted; alkyl groups, which may themselves be substituted; and aryl groups, which may themselves be substituted, such as phenyl and substituted phenyl. Alkyl includes substituted and unsubstituted benzyl. Reference in the present specification to alkoxy and aryloxy groups means alkyl-O- and aryl-O- groups, respectively. Reference to alkoyl and aryloyl groups means alkyl-CO- and aryl-CO-, respectively.

25 [0014] Reference in the present specification to heterocyclic groups means groups containing one or more, optionally bridged, rings containing 1 to 6 heteroatoms in total. Each ring in the group may contain 3 to 12, preferably 1 to 6, atoms in total. At least one ring present contains 1 to 2 heteroatoms. Where two or more rings are present they may be fused or unfused. The rings can contain unsaturation. Heteroatoms includes O, S and N. Examples of such heterocyclic groups containing one or more pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, thionaphthyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl and carbolinyl.

35 [0015] References in the present specification to polycyclic groups means a group comprising two or more non-aromatic carbocyclic or heterocyclic rings which may themselves be substituted. Preferably the group contains 2 to 4 fused or non-fused rings, each ring suitably containing 3 to 12 atoms, more suitably 4 to 10, more suitably 5 to 7, and even more suitably 5 to 6 atoms. The definitions of cyclic alkyl and heterocyclic rings given above also apply to the rings in the polycyclic groups.

40 [0016] Reference in the present specification to halogen means a fluorine, chlorine, bromine or iodine radical, preferably fluorine or chlorine radical.

[0017] The group Ar comprises a substituted or unsubstituted aryl group, wherein the term "aryl group" and the possible substitution of said group is as defined above. Preferably, Ar is a substituted or unsubstituted phenyl group. Particularly preferred substituents are electron withdrawing groups such as halogen (preferably chlorine or fluorine), trihalomethyl (preferably trifluoromethyl), cyano and nitro groups. Preferably, Ar is phenyl, 3,5-dichloro-phenyl, p-trifluoromethyl-phenyl, p-cyano-phenyl, or p-nitro-phenyl.

[0018] R³ is selected from hydrogen, alkyl, aryl, heterocyclic and polycyclic groups.

[0019] Preferably, R³ is a substituted or unsubstituted alkyl group. Preferably, R³ is a substituted or unsubstituted C₁₋₆ alkyl group, more preferably an ethyl or methyl group.

50 [0020] Preferably, R³ is selected from the group comprising -CH₃, -C₂H₅ and -CH₂Ph.

[0021] Preferably, at least one of R¹ and R² is hydrogen. It will be appreciated that if R¹ and R² are different, the carbon atom to which they are bonded is an asymmetric centre.

[0022] Preferably this carbon atom is chiral. When this carbon atom is chiral, the stereochemistry at this site may be D or L or mixed, with L-stereochemistry being preferred.

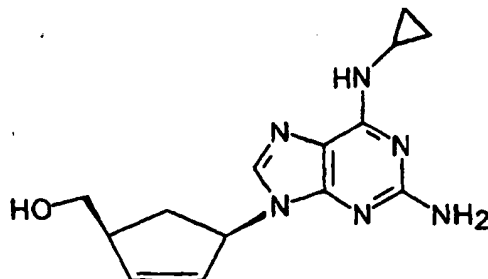
55 [0023] Suitably, R¹ and R² are the same or different and are H, -CH₃ or -C₂H₅. Preferably, R¹ is H and R² is -CH₃, -CH₂CH₃ or CH₂Ph.

[0024] R⁵ and R¹ can be linked to form an alkylene bridge comprising 3 to 4 carbon atoms so as to form a 5- or 6-membered ring. Preferably R⁵ is hydrogen.

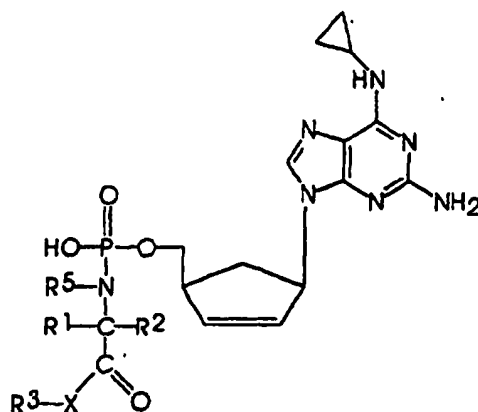
EP 1 117 669 B1

[0025] It will be appreciated that the group $\text{-NH-CHR}^1\text{-CO}_2\text{R}^3$ corresponds to a carboxy-protected α -amino acid. Preferably, the group R^1 corresponds to the side chain of a naturally occurring amino acid such as Alanine, Arginine, Asparagine, Aspartic Acid, Cysteine, Cystine, Glycine, Glutamic Acid, Glutamine, Histidine, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, Valine. Preferably, R^1 is Me or PhCH_2 corresponding to the side chain of alanine or phenylalanine, respectively. Preferably, the stereochemistry at the asymmetric centre $\text{-CHR}^1\text{-}$ corresponds to an L-amino acid.

[0026] It is a feature of the aryl ester phosphate compounds of the present invention that they exhibit significantly enhanced anti-viral efficacy in *in vitro* tests, in comparison to their corresponding nucleoside analogue, (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol, which is known as Abacavir and which has the following structural formula:



[0027] According to a further aspect of the present invention there is provided a compound of formula (II):



wherein R^1 , R^2 , R^3 , R^5 and X are as defined above, or a pharmaceutically acceptable derivative or metabolite thereof. Preferably X is O .

[0028] The intracellular generation of such anti-viral metabolites is an important feature of the invention for several reasons. In cases where the nucleoside is not a good substrate for host nucleotide kinases, activation will be poor and anti-viral efficacy low, even if the triphosphate is an excellent RT inhibitor. In such cases, the generation of the present metabolites may lead to a very significant enhancement in anti-viral action.

[0029] By "a pharmaceutically acceptable derivatives" is meant any pharmaceutically acceptable salt, ester or salt of such ester or any other compound which upon administration to a recipient is capable of providing (directly or indirectly) a compound of the present formula or present metabolite. Preferred "pharmaceutically acceptable derivatives" include sodium, succinate, fumarate, glutarate and D-tartrate salts.

[0030] By "pharmaceutically acceptable metabolite" is meant a metabolite or residue of a compound of the present formula or present metabolite which gives rise to reverse transcriptase inhibition exhibited by the present compounds.

[0031] According to a further aspect of the present invention there is provided a compound according to the present

EP 1 117 669 B1

invention for use in a method of treatment, prophylaxis or diagnosis, preferably in the prophylaxis or treatment of viral infection.

[0032] According to a further aspect of the present invention there is provided use of a compound according to the present invention in the manufacture of a medicament for the prophylaxis or treatment of viral infection.

5 **[0033]** A method of prophylaxis or treatment of viral infection can comprise administration to a patient in need of such treatment an effective dose of a compound according to the present invention.

[0034] The viral infection may comprise any viral infection such as HIV and herpes virus, including HSV 1 and HSV 2, CMV, VZV, EBV, HAV, HBV, HCV, HDV, HHV6, HHV7, HHV8, papilloma, adenoviruses, rabies and influenza.

10 **[0035]** Preferably, the viral infection comprises HIV or HBV infection, more preferably HIV-I or HIV-II. It is a feature of the present invention that the compounds exhibit good activity against HIV-I and HIV-II, and HBV.

[0036] According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound of the present invention in combination with a pharmaceutically acceptable excipient.

15 **[0037]** According to a further aspect of the present invention there is provided a method of preparing a pharmaceutical composition comprising the step of combining a compound of the present invention with a pharmaceutically acceptable excipient.

[0038] Compounds of the present invention can demonstrate significant stability towards acid-mediated hydrolytic decomposition. The present compounds can thus be particularly suitable for oral administration under typical dosing conditions in humans as they can retain stability under the highly acidic environment of the stomach.

20 **[0039]** As the purine in compounds of formula (I) is a weak base ($pK_a=5.0$) and the compounds of formula (I) demonstrate stability to acids, salts can be formed of compounds of formula (I) with acids, such as carboxylic acids and dicarboxylic acids. Such salts can be stable, crystalline solids, which can be beneficial in terms of improved shelf-life and ease of handling during manufacture into pharmaceutical compositions. Preferred carboxylic and dicarboxylic acids include malonic, succinic, glutaric, fumaric and tartaric acids. In contrast to the salts of compounds of formula (I), the free bases of compounds of formula (I) can be in a non-crystalline amorphous form which can be hygroscopic.

25 **[0040]** The P-OH group of compounds of formula (II) is a weak acid and can therefore form monobasic salts with bases to give, for example, sodium, potassium, ammonium, and triethylammonium salts. In compounds of formula (II) when X is OH, dibasic salts can be formed. Such dibasic salts can be in the form of stable solids, which can provide benefits of improved shelf-life and ease of handling during manufacture into pharmaceutical compositions.

30 **[0041]** Compounds of the present invention can also demonstrate enhanced stability in biological media, for example, in human plasma. The increased half-life of compounds embodying the present invention in media such as human plasma may permit a pharmacokinetic advantage in dosing in humans in need of treatment.

[0042] The medicament employed in the present invention can be administered by oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous, transdermal, airway (aerosol), rectal, vaginal and topical (including buccal and sublingual) administration.

35 **[0043]** For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules, as a powder or granules, or as an aqueous solution or suspension.

[0044] Tablets for oral use may include the active ingredients mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

40 **[0045]** Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredients is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

[0046] Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

45 **[0047]** Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

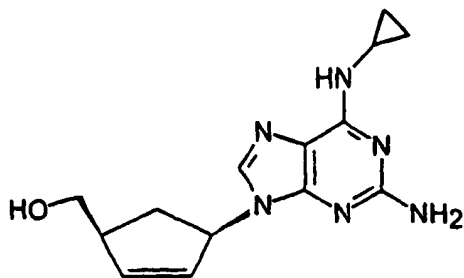
50 **[0048]** For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinylpyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

55 **[0049]** The compounds of the invention may also be presented as liposome formulations.

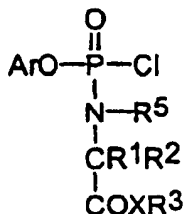
EP 1 117 669 B1

[0050] In general a suitable dose will be in the range of 0.01 to 10 mg per kilogram body weight of the recipient per day, preferably in the range of 0.2 to 1.0 mg per kilogram body weight per day. The desired dose is preferably presented once daily, but may be dosed as two, three, four, five or six or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing 10 to 1500 mg, preferably 20 to 1000 mg, and most preferably 50 to 700 mg of active ingredient per unit dosage form.

[0051] According to a further aspect of the present invention there is provided a process for the preparation of the present compound comprising reaction of a compound of formula



with a compound of formula



wherein R^1 , R^2 , R^3 , R^5 and X have the meanings given above.

[0052] The reaction may be carried out under dry conditions at ambient temperature in tetrahydrofuran in the presence of *N*-methylimidazole, or by using *t*-butyl magnesium chloride and an excess of the appropriate phosphorochloridate reagent.

[0053] Compounds embodying the present invention wherein *Ar* is replaced by *H* may be prepared from the acid form by treatment of the ester with an aqueous base.

[0054] Compounds wherein X is NH or NR^4 can be prepared by treating the acid form ($X = O$ and $R^3 = H$) with amine.

[0055] The above starting material, (1*S*, 4*R*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol, is known as Abacavir and may be made by any procedure known in the art, for example by procedures described in European Patent Specification Number 0434450, PCT Patent Application No. PCT/GB95/02014, and PCT Patent Application No. PCT/EP98/02835.

[0056] The invention will now be described with reference to the following Examples. It will be appreciated that what follows is by way of example only and that modifications to detail may be made whilst still falling within the scope of the invention.

EXPERIMENTAL PROCEDURES

General methods

[0057] The following anhydrous solvents and reagents were bought dry from Aldrich with sure seal stoppers: Dichloromethane (DCM), diethyl ether (Et_2O), tetrahydrofuran (THF), *N*-methyl imidazole (NMI), methanol (MeOH), dimethylformamide (DMF), pyridine (pyr), dioxane, and *t*BuMgCl. Triethylamine (NEt_3) was dried by refluxing over CaH_2 for several hours and then distilled off for immediate use.

EP 1 117 669 B1

Chromatography

[0058] Thin layer chromatography (tlc) was performed on commercially available Merck Kieselgel 60F₂₅₄ (product name) plates and the separated components were visualised using ultra violet light (254nm and 366nm), or by treatment with a 5% ethanolic solution of dodeca-molybdo-phosphoric acid (MPA) followed by heating. Column chromatography was performed using Woelm silica (32-63mm) as the stationary phase.

Spectral Characterisation

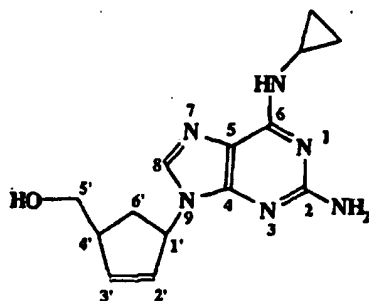
[0059] All NMR spectral data, unless otherwise stated, were obtained in CDCl₃. Proton and Carbon-13 nuclear magnetic resonance were recorded on a Bruker Avance DPX300 (product name) spectrometer with operating frequencies of 300MHz and 75MHz respectively. Phosphorous-31 NMR spectra were recorded on a Bruker Avance DPX300 spectrometer operating at 121MHz, and are reported in units of δ relative to 85% phosphoric acid as the external standard, positive shifts are downfield. The following abbreviations are used in the assignment of NMR signals: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad signal), dd (double of doublets), dt (double of triplets).

[0060] Low resolution mass spectra were run on a VG Platform II Fisons instrument (Fisons, Altrincham, UK) (atmospheric pressure ionization, electrospray mass spectrometry) in either negative or positive ion mode.

[0061] High Performance Liquid Chromatography (HPLC) was performed on an SSODS2 (product name) reverse phase column with an eluent of water/acetonitrile. 100% water (0 mins), 20% water (35mins), 20% water (45mins), 100% water (55mins), with a flow rate of 1 ml/min and detection by UV at 254 nm. Standards: acetone (t_R 4.54mins), toluene (t_R 10.21mins). Final products showed purities >99%, with undetectable amounts of the parent nucleoside.

Nomenclature and Numbering of Compounds

[0062] IUPAC nomenclature is used where possible, but for ease some compounds are abbreviated. Numbering is by conventional nucleoside numbering.



Standard Procedures

[0063] For practical purposes, standard procedures are given where applicable.

Standard Procedure 1

[0064] To a stirring solution of anhydrous alcohol (10mol eq) was added thionyl chloride (2mol eq) dropwise at 0°C, and the resulting solution stirred for 1hr. Upon rising to room temperature, the appropriate amino acid (1mol eq) was added and the reaction heated at reflux for 6-16hrs. Removal of the solvent and recrystallisation from methanol:ether gave the amino ester hydrochloride salts.

Standard Procedure 2

[0065] The appropriate amino acid (1mol eq), *para*-toluene sulfonic acid (1.1mol eq) and the appropriate alcohol (1mol eq) were heated under reflux in toluene (100ml), under Dean and Stark conditions, for 6-16hrs. On cooling to room temperature the solvent was removed under reduced pressure to give an oil. This was solubilised in dichloromethane (50ml) and washed with 10% K₂CO₃ (50ml), and water (50ml), filtered and the filtrate reduced to dryness to give

EP 1 117 669 B1

an oil. This was solubilised in the minimum amount of acetone and neutralised with 2M HCl, and then lyophilised to give the amino acid ester hydrochloride salts.

Standard procedure 3

5

[0066] Phenyl dichlorophosphate (1mol eq) and the appropriate amino acid ester hydrochloride salt (1mol eq) were suspended in anhydrous dichloromethane (30-60ml). Anhydrous triethylamine (2mol eq) in anhydrous dichloromethane (30ml) was added dropwise at -80°C, and the reaction left to rise to room temperature overnight. The solvent was removed under reduced pressure, and under nitrogen, to give white solids. This was washed with anhydrous ether (2x25ml), filtered and the filtrate reduced to dryness to give the products as crude oils. These were stored in anhydrous THF and used without any further purification.

10

Standard Procedure 4

15

[0067] (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (1mol eq) was dried by azeotropeing with anhydrous pyridine (3x5ml), and then suspended in anhydrous THF (5-30ml). To the suspension was added tBuMgCl (1-2mol eq, 1.0M solution in THF) dropwise, and the resulting suspension stirred for 10mins. The phosphorochloridate species (3mol eq, solution in THF) was then added dropwise and the resulting solution stirred at room temperature for 24-96hrs. The reaction was then quenched by the addition of sat. NH₄Cl (0.1ml), and after 10mins the solvent was removed under reduced pressure. The crude product was purified by silica column chromatography.

20

L-Alanine methyl ester hydrochloride.

C₄H₁₀O₂N₁Cl₁, MW=139.38.

25

[0068] This was synthesised according to Standard Procedure 1, using anhydrous methanol (34ml, 0.84mol), thionyl chloride (8.2ml, 0.112mol) and L-alanine (5.0g, 0.056mol). The product was isolated as a white solid (2.87g, 36.7%).
¹H NMR (D₂O): δ 4.07-4.00 (1H,q,CH₂,J=7.22Hz), 3.83 (3H,s,OCH₃), 1.39-1.37 (3H,t,CH₃).
¹³C NMR (D₂O): δ 171.5 (C=O), 53.9 (OCH₃), 49.1 (CH), 15.4 (CH₃).

30

Phenyl-(methoxy-L-alaninyl)-phosphorochloridate.

C₁₀H₁₃O₄N₁Cl₁P₁, MW=277.65.

35

[0069] This was synthesised according to Standard Procedure 3, using L-Alanine methyl ester hydrochloride (2.0g, 14.34mmol), phenyl phosphorodichloridate (3.02g, 2.14ml, 14.34mmol) and anhydrous triethylamine (2.90g, 4.0ml, 28.68mmol). The product (3.91g, 98.2%) was isolated as a colourless crude oil which was stored in anhydrous THF (40ml) to give a 0.47M solution.

40

³¹P NMR: δ 9.28, 8.97 (1:1).
¹H NMR: δ 7.39-7.34 (2H,m,'o'-Ph), 7.29-7.20 (3H,m,'m'+p'-Ph), 4.49-4.37 (1H,q,NHala), 4.27-4.09 (1H,m,CHala), 3.78 (3H,d,OCH₃), 1.52-1.49 (3H,dd,CH₃).
¹³C NMR: 173.6 (CO), 150.1 ('ipsd'-Ph), 130.25 ('m'-Ph), 126.4 ('p'-Ph), 120.9 ('o'-Ph), 53.2 (OCH₃), 51.0 (CH), 20.9 (CH₃ala).

45

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(methoxy-L-alaninyl)]-phosphate. C₁₁490.

C₂₄H₃₀O₅N₇P₁, MW=527.53.

50

[0070] This was synthesised according to Standard Procedure 4, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (500mg, 1.75mmol), tBuMgCl (1.0M solution in THF) (1.75ml, 1.75mmol) and phenyl-(methoxy-L-alaninyl)-phosphorochloridate (0.47M solution in THF) (11.17ml, 5.24mmol), in THF (30ml) and stirring at room temperature for 70hrs. The crude product was purified by column chromatography eluting with 3% MeOH in DCM and then 2% MeOH in DCM to give the product as a white foam (442mg, 48%).

55

³¹P NMR (MeOH-d₄): δ 3.97, 3.88.
¹H NMR: δ 7.41 (1H,d,C8), 7.24-7.19 (2H,m,'o'-Ph), 7.13-7.03 (3H,m,'m'+p'-Ph), 6.08 (1H,bs,NH), 5.98 (1H,q,H2'), 5.78 (t,H3'), 5.44 (1H,t,H1'), 5.09 (2H,bs,NH₂), 4.22-4.02 (3H,m,NHala+H5'), 3.99-3.87 (1H,m,CHala), 3.59 (3H,t,OCH₃), 3.05 (1H,d,H4'), 2.92 (1H,bs,CHcPr), 2.73-2.62 (1H,m,1of H6'), 1.62-1.53 (1H,m,1of H6'), 1.30-1.25 (3H,t,

EP 1 117 669 B1

CH₃ala), 0.78-0.71 (2H,q,2H of CH₂cPr), 0.54-0.49 (2H,t,2H of CH₂cPr).

¹³C NMR: δ 174.6 (C=O), 160.3 (C2), 156.6 (C4), 151.3 (C6), 151.1 ('*ipso*'-Ph), 136.8 (C8), 135.9 (C2'), 131.5 (C3'), 130.0 ('*m*'-Ph), 125.2 ('*p*'-Ph), 120.5 ('*o*'-Ph), 115.0 (C5), 69.2 (C5'), 59.2 (C1'), 52.8 (OCH₃), 50.5 (CHala), 46.0 (C4'), 34.9 (C6'), 24.2 (CHcPr), 21.2 (CH₃ala), 7.7 (CH₂cPr).

5 MS ES⁺: m/z 527.86 (100%) (M)⁺, 546.84 (M+K)⁺.

MS FAB: For C₂₄H₃₁O₅N₇P, requires 528.212431, found 528.213848.

HPLC: t_R 30.33 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

10 IR: 3328.6 (N-Hstr.), 2922.1, 2862.9 (C-Hstr.), 1734.4 (C=Ostr.), 1590.9 (aromatic C-Cstr.), 1462.9 (C-Hdef.), 1376.8 (-CH₃sym.def.), 1207.1 (P-O-aryl), 1154.0 (C-Ostr.), 1027.7 (P-O-alkyl), 933.4 (olefinic C-Hdef.), 721.8 (monosub. aromatic C-Hdef.).

Phenyl-(methoxy-D-alaninyl)-phosphorochloridate.

C₁₀H₁₃O₄N₁Cl₁P₁, MW=277.65.

15

[0071] This was synthesised according to **Standard Procedure 3**, using D-alanine methyl ester hydrochloride (1.0g, 7.17mmol), PhOP(O)Cl₂ (1.51g, 1.07ml, 7.17mmol) and NEt₃ (1.45g, 2.0ml, 14.0mmol) to yield 1.66g (83.4%) of crude product that was stored in anhydrous THF (10ml), to give a 0.60mmol/ml solution that was used without further purification.

20 ³¹P NMR: δ 9.38, 9.18 (1:1).

¹H NMR: δ 7.39-7.30 (2H,t,'*o*'-Ph), 7.29-7.09 (3H,m,'*m*'+'*p*'-Ph), 4.85-4.80 (1H,d,NHala), 4.19-4.11 (1H,m,CHala), 3.75 (3H,d,OCH₃), 1.52-1.49 (3H,dd,CH₃ala).

¹³C NMR: δ 173.6 (C=O), 150.1 ('*ipso*'-Ph), 130.3 ('*o*'-Ph), 126.4 ('*p*'-Ph), 120.9 ('*m*'-Ph), 53.2 (OCH₃), 50.9 (CHala), 21.0 (CH₃ala).

25

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(methoxy-D-alaninyl)]-phosphate. Cf1583.

C₂₄H₃₀O₅N₇P₁, MW=527.53.

30

[0072] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (400mg, 1.4mmol), tBuMgCl (1.0M solution in THF) (2.1ml, 2.1mmol), and phenyl-(methoxy-D-alaninyl)-phosphorochloridate (0.6M solution in THF) (7.0ml, 4.19mmol) in THF (25ml) stirring at room temperature for 36hrs. The crude product was purified by eluting with 3% MeOH in CHCl₃ and then 2.5% MeOH in CHCl₃ to give the product as a white foam (318.6mg, 43.2%).

35

³¹P NMR: δ 3.93, 3.70.

¹H NMR: δ 7.56+7.51 (1H,d,H8), 7.37-7.32 (2H,m,'*o*'-Ph), 7.29 (1H,d,'*p*'-Ph), 7.25-7.15 (2H,m,'*m*'-Ph), 6.10 (1H,t, J=5.28Hz,H2'), 6.03 (1H,bs,NHcPr), 5.94-5.89 (1H,m,H3'), 5.54 (1H,bs,H1'), 5.01 (2H,bs,NH₂), 4.26-3.83 (4H,m,CHala,NHala+H5'), 3.72 (3H,d,OCH₃), 3.18 (1H,s,CHcPr), 3.02 (1H,bs,H4'), 2.86-2.75 (1H,m,1 of H6'), 1.78-1.64 (1H,m, 1 of H6'), 1.39-1.36 (3H,dd,CH₃ala), 0.90-0.83 (2H,q,J=6.13Hz,2H of CH₂cPr), 0.63 (2H,bs, 2H of CH₂cPr).

40

¹³C NMR: δ 174.5 (CO), 160.3 (C2), 156.6 (C4) 151.2 (C6), 151.0 ('*ipso*'-Ph), 136.8 (C2'), 136.1 (C8), 131.5 (C3'), 130.0 ('*m*'-Ph), 125.3 ('*p*'-Ph), 120.5 ('*o*'-Ph), 115.2 (C5), 69.3 (C5'), 59.3 (C1'), 52.9 (CHala), 50.5 (OCH₃), 46.0 (C4'), 34.9 (C6'), 24.1 (CHcPr), 21.4 (CH₃ala), 7.8 (CH₂cPr).

MS ES⁺: m/z 527.86 (100%) (M)⁺, 546.84 (M+K)⁺.

45

MS FAB: For C₂₄H₃₁O₅N₇P requires 528.212431, found 528.211505.

HPLC: t_R 29.807 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

IR: 3333.6 (N-Hstr.), 2923.4, 2853.4 (C-Hstr.), 1734.1 (C=Ostr.), 1591.1 (aromatic C-Cstr.), 1458.3 (C-Hdef.), 1376.7 (-CH₃sym.def.), 1208.3 (P-O-aryl), 1153.3 (C-Ostr.), 1026.9 (P-O-alkyl), 931.9 (olefinic C-Hdef.), 721.6 (monosub. aromatic C-Hdef.).

50

Phenyl-(methoxy-L-phenylalaninyl)-phosphorochloridate.

C₁₆H₁₇O₄N₁Cl₁P₁, MW=353.74.

55

[0073] This was synthesised according to **Standard Procedure 3**, using L-phenylalanine methyl ester (1.0g, 4.64mmol), PhOP(O)Cl₂ (0.98g, 0.70ml, 4.64mmol) and NEt₃ (0.94g, 1.30ml, 9.28mmol) to yield 1.45g (88.4%) of crude product as an oil that was stored in anhydrous THF (10ml), to give a 0.41mmol/ml solution that was used without further purification.

EP 1 117 669 B1

³¹P NMR: δ 9.37, 9.23 (1:1).

¹H NMR: δ 7.60-7.16 (10H,m,2xPh), 4.70-4.49 (1H,m,CHala), 4.38-4.16 (1H,m,NHala), 3.89 (3H,d,OCH₃), 3.23 (2H,m,CH₂Ph).

- 5 (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(methoxy-L-phenylalaninyl)]-phosphate. Cf1585.

C₃₁H₃₄O₅N₇P₁, MW=603.6.

- 10 [0074] This was synthesised according to Standard Procedure 4, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (300mg, 1.05mmol), tBuMgCl (1.0M solution in THF) (1.57ml, 1.57mmol) and phenyl-(methoxy-L-phenylalaninyl)-phosphorochloridate (0.41M solution in THF) (7.66ml, 3.14mmol) in THF (20ml) stirring at room temperature for 48hrs. The crude product was purified by eluting with 3% MeOH in CHCl₃ and then 2.5% MeOH in CHCl₃ to give the product as a white foam (272.9mg, 43.15%).

- 15 ³¹P NMR: δ 3.91, 3.80.

¹H NMR: δ 7.47+7.43 (1H,d,H8), 7.31-7.06 (10H,m,2xPh), 6.25 (1H,d,NHcPr), 6.00-5.95 (1H,q,H^{2'}), 5.87-5.81 (1H,t,H^{3'}), 5.49 (1H,s,H^{1'}), 5.19 (2H,bs,NH₂), 4.31-3.92 (4H,m,CHala,NHala+H^{5'}), 3.64 (3H,d,OCH₃), 3.02-2.89 (4H,m,CH₂Ph,CHcPr+H^{4'}), 2.78-2.63 (1H,m,1 of H^{6'}), 1.63-1.49 (1H,m,1 of H^{6'}), 0.86-0.80 (2H,q,J=6.24Hz,2H of CH₂cPr), 0.60 (2H,d,2H of CH₂cPr).

- 20 ¹³C NMR: δ 174.3 (CO), 161.5 (C2), 157.7 (C4), 152.4 (C6), 152.1 ('*ipso*'-OPh), 137.7 ('*ipso*'-Bn), 137.1 (C2'), 136.9 (C8), 132.4 (C3'), 130.9 ('*o*'+'*m*'-Bn), 129.9 ('*m*'-OPh), 128.4 ('*p*'-Bn), 126.2 ('*p*'-OPh), 121.5 ('*o*'-OPh), 116.1 (C5), 70.1 (C5'), 60.1 (C1'), 57.2 (CHala), 53.6 (OCH₃), 46.9 (C6'), 41.7 (C4'), 35.9 (CH₂Ph), 25.1 (CHcPr), 8.7 (CH₂cPr).

MS ES⁺: m/z 603.8 (100%, M⁺), 604.8 (35%, M+H⁺), 625.7 (15%, M+Na⁺).

MS FAB: For C₃₁H₃₄O₅N₇P requires 604.243731, found 604.242585.

- 25 HPLC: t_R 34.707, 35.020 (100%)-(100% water (0mins) 20% water (35mins), 20% water (45mins), 100% water (55mins)).

IR: 3331.7 (N-Hstr.), 3007.2, 2952.2 (C-Hstr.), 1741.1 (C=Ostr.), 1595.6, 1487.7 (aromatic C-Cstr.), 1455.0 (C-Hdef.), 1393.9 (-CH₃sym.def.), 1252.5 (P=O), 1214.3 (P-O-aryl), 1125.3 (C-Ostr.), 1025.6 (P-O-alkyl), 935.8 (olefinic C-Hdef.), 754.8 (monosub.aromatic C-Hdef.).

30

Pbenyl-(methoxyglycinyl)-phosphorochloridate.

C₉H₁₁O₄N₁Cl₁P₁, MW=263.62.

- 35 [0075] This was synthesised according to Standard Procedure 3, using glycine methyl ester (1.5g, 11.9mmol), PhOP(O)Cl₂ (2.52g, 1.79ml, 11.9mmol) and NEt₃ (2.42g, 3.33ml, 23.9mmol) to yield 3.07g (97.15%) of crude product as an oil that was stored in anhydrous THF (15ml), to give a 0.774mmol/ml solution that was used without further purification.

³¹P NMR: δ 10.43.

- 40 ¹H NMR: δ 7.43-7.38 (2H,m,'*o*'-Ph), 7.31-7.25 (3H,m,'*m*'+'*p*'-Ph), 4.67 (1H,bs,NHala), 3.94 (2H,dd,CH₂), 3.83 (3H,s,OCH₃).

¹³C NMR: δ 170.4 (CO), 150.1 ('*ipso*'-Ph), 130.2 ('*m*'-Ph), 126.4 ('*p*'-Ph), 120.8 ('*o*'-Ph), 53.1 (OCH₃), 43.4 (CH₂).

- 45 (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(methoxy-glycinyl)]-phosphate. Cf1588.

C₂₃H₂₈O₅N₇P₁, MW=513.49.

- 50 [0076] This was synthesised according to Standard Procedure 4, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (300mg, 1.05mmol), tBuMgCl (1.0M solution in THF) (1.57ml, 1.57mmol) and phenyl-(methoxy-glycinyl)-phosphorochloridate (0.774M solution in THF) (4.06ml, 3.14mmol) in THF (20ml) stirring at room temperature for 96hrs. The crude product was purified by eluting with 3% MeOH in CHCl₃ and then with 2.5% MeOH in CHCl₃ to give the product as a white foam (82.6mg, 15.4%).

- 55 ³¹P NMR: δ 4.79, 4.67 (1:1).

¹H NMR: δ 7.40+7.36 (1H,d,H8), 7.24-7.19 (2H,t,'*o*'-Ph), 7.15-7.10 (2H,t,'*m*'-Ph), 7.07-7.02 (1H,t,'*p*'-Ph), 6.00-5.96 (2H,m,H^{2'}+NHcPr), 5.80-5.76 (1H,m,H^{3'}), 5.45-5.41 (1H,t,H^{1'}), 4.99 (2H,bs,NH₂), 4.14-4.00 (3H,m,NHala+H^{5'}), 3.62 (3H,s,OCH₃), 3.03 (1H,d,H^{4'}), 2.91 (1H,d,CHcPr), 2.73-2.62 (1H,m,1 of H^{6'}), 1.62-1.51 (1H,m,1 of H^{6'}), 1.45-1.43 (6H,t,2xCH₃), 0.78-0.71 (2H,q,2H of CH₂cPr), 0.54-0.49 (2H,t,2H of CH₂cPr).

EP 1 117 669 B1

¹³C NMR: δ 172.1 (C=O), 160.2 (C2), 156.6 (C4), 152.0 (C6), 151.7 (*ipso*-Ph), 137.7 (C8), 137.1 (C2'), 132.0 (C3'), 130.8 (*m*-Ph), 126.0 (*p*-Ph), 121.2 (*o*-Ph), 115.5 (C5), 69.9 (C5'), 60.0 (C1'), 53.5 (OCH₃), 46.7 (C4'), 43.9 (CH₂), 35.4 (C6'), 25.0 (CHcPr), 8.5 (CH₂cPr).

MS ES⁺: m/z 513.9 (100%, M⁺), 514.8 (25%, M+H⁺), 535.8 (40%, M+Na⁺).

5 MS FAB: For C₂₃H₂₉O₅N₇P requires 514.196781, found 514.195321.

HPLC: t_R 28.419 (99.9%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

IR: 3342.0 (N-Hstr.), 1749.8 (C=Ostr.), 1596.2, 1488.4 (aromatic C-Cstr.), 1451.9 (C-Hdef.), 1394.7 (-CH₃sym.def.), 1259.6 (P=O), 1212.1 (P-O-aryl), 1151.6 (C-Ostr.), 1026.8 (P-O-alkyl), 937.8 (olefinic C-Hdef.), 760.7 (monosub.aromatic C-Hdef.).

10

Methyl-2-amino-2-methylpropanoate hydrochloride.

C₅H₁₂O₂N₁Cl₁, MW=153.61.

15 **[0077]** This was synthesised according to **Standard Procedure 1**, using 2-amino-isobutyric acid (4g, 0.039mol) with thionyl chloride (5.66ml, 0.078mol) and anhydrous methanol (23.5ml, 0.58mol). This gave the product as a white solid (5.805g, 97.4%).

¹H NMR (DMSO): δ 8.85 (3H,s,NH₃⁺Cl⁻), 3.72 (3H,s,OMe), 1.48 (6H,s,2xMe).

¹³C NMR (DMSO): δ 172.8 (C=OOMe), 56.6 (OMe), 53.9 (CMe₂), 24.1 (2xMe).

20 MS ES⁺: m/z 117.71 M+H⁺, 142.88 M+Na⁺.

Phenyl-(methyl-2-amino-2-methylpropanoate)-phosphorochloridate.

C₁₁H₁₅O₄N₁Cl₁P₁, MW=291.67.

25

[0078] This was synthesised according to **Standard Procedure 3**, using 2-amino-isobutyrate methyl ester hydrochloride (1.0g, 6.51mmol), PhOP(O)Cl₂ (1.37g, 0.97ml, 6.51mmol) and NEt₃ (1.32g, 1.18ml, 13.02mmol), to yield 1.73g (91%) of the crude product as an oil. This was stored in anhydrous THF (10ml) to give a solution of 0.593mmol/ml, and used without further purification.

30 ³¹P NMR: δ 6.86.

¹H NMR: δ 7.43-7.38 (2H,t,*o*-Ph), 7.32-7.21 (3H,m,*m'*-*p'*-Ph), 4.84 (1H,d,NHala), 3.83 (3H,s,OCH₃), 1.72 (6H,d,2xCH₃).

¹³C NMR: δ 175.7 (CO), 150.3 (*ipso*-Ph), 130.3 (*m*-Ph), 126.3 (*p*-Ph), 121.0 (*o*-Ph), 58.8 (OCH₃), 53.6 (C[CH₃]₂), 27.3 + 27.0 (2xCH₃).

35

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(methoxy-α,αdimethylglycyl)]-phosphate. Cf1584.

C₂₅H₃₂O₅N₇P₁, MW=542.23.

40

[0079] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (300mg, 1.05mmol), tBuMgCl (1.0M solution in THF) (1.57ml, 1.57mmol) and phenyl-(methoxy-dimethylglycyl)-phosphorochloridate (0.59M solution in THF) (5.3ml, 3.14mmol) in THF (20ml) stirring at room temperature for 96hrs. The crude product was purified by eluting with 3% MeOH in CHCl₃ and then with 2.5% MeOH in CHCl₃ to give the product as a white foam (193.7mg, 34.14%).

45 ³¹P NMR: δ 2.49.

¹H NMR: δ 7.40+7.36 (1H,d,H8), 7.24-7.19 (2H,t,*o*-Ph), 7.15-7.10 (2H,t,*m'*-Ph), 7.07-7.02 (1H,t,*p'*-Ph), 6.00-5.96 (2H,m,H2'+NHcPr), 5.80-5.76 (1H,m,H3'), 5.45-5.41 (1H,t,H1'), 4.99 (2H,bs,NH₂), 4.14-4.00 (3H,m,NHala+H5'), 3.62 (3H,s,OCH₃), 3.03 (1H,d,H4'), 2.91 (1H,d,CHcPr), 2.73-2.62 (1H,m,1of H6'), 1.62-1.51 (1H,m,1of H6'), 1.45-1.43 (6H,t,2xCH₃), 0.78-0.71 (2H,q,2H of CH₂cPr), 0.54-0.49 (2H,t,2H of CH₂cycl.).

50

MS ES⁺: m/z 541.9 (100%, M⁺), 563.8 (30%, M+Na⁺).

MS FAB: For C₂₅H₃₃O₅N₇P requires 542.228081, found 542.228428.

HPLC: t_R 28.347 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

55 IR: 3346.0 (N-Hstr.), 2923.0, 2853.5 (C-Hstr.), 1734.0 (C=Ostr.), 1590.2 (aromatic C-Cstr.), 1458.4 (C-Hdef.), 1376.8 (-CH₃sym.def.), 1261.3 (P=O), 1152.7 (C-Ostr.), 1028.0 (P-O-alkyl), 936.0 (olefinic C-Hdef.), 721.7 (monosub.aromatic C-Hdef.).

EP 1 117 669 B1

L-Aspartic acid dimethyl ester hydrochloride.**C₆H₁₂O₄N₁Cl₁, MW=197.62.**

5 [0080] This was synthesised according to **Standard Procedure 1**, using L-asparagine (2.5g, 0.019mol) with thionyl chloride (3.67ml, 0.042mol) and anhydrous methanol (12.86ml, 0.32mol). This gave L-aspartic acid dimethyl ester hydrochloride in 3.70g, 99% yield.

¹H NMR (MeOH-d₄): δ 4.53-4.50 (1H,t,CH), 3.94 (3H,s,OCH₃), 3.85 (3H,s,OCH₃), 3.18 (2H,d,CH₂).

¹³C NMR (MeOH-d₄): δ 170.4, 168.4 (CO), 53.0+52.0 (2xOMe), 49.4 (CH), 33.8 (CH₂).

10

Phenyl-(dimethoxy-L-aspartyl)-phosphorochloridate.**C₁₂H₁₅O₆N₁Cl₁P₁, MW=335.68.**

15 [0081] This was synthesised according to **Standard Procedure 3**, using L-Aspartic acid dimethyl ester (1.0g, 5.04mmol), PhOP(O)Cl₂ (1.06g, 0.75ml, 5.04mmol) and NEt₃ (1.02g, 1.40ml, 10.1mmol) to yield 0.55g (32.4%) of crude product as an oil that was stored in anhydrous THF (5ml), to give a 0.33mmol/ml solution that was used without further purification.

³¹P NMR: δ 9.74, 9.59 (1:1).

20

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(L-aspartic acid dimethyl ester)]-phosphate. Cf1 589.

C₂₄H₃₀O₅N₇P₁, MW=527.53.

25

[0082] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (250mg, 0.87mmol), tBuMgCl (1.0M solution in THF) (0.87ml, 0.87mmol) and phenyl-(L-aspartic acid dimethyl ester)-phosphorochloridate (0.50M solution in THF) (5.20ml, 2.62mmol) in THF (15ml) and stirring at room temperature for 48hrs. The crude product was purified by eluting with 2.5% MeOH in CHCl₃ (x2) to give the product as a pale yellow foam (163.5mg, 32.0%).

30

³¹P NMR: δ 4.19, 3.76 (1:1).

¹H NMR: δ 7.40 (1H,d,H8), 7.24-7.19 (2H,t,'*o*'-Ph), 7.12-7.03 (3H,m,'*m*'+'*p*'-Ph), 6.05-5.95 (2H,m,H2'+NHcPr), 5.79 (1H,d,H3'), 5.44 (1H,s,H1'), 5.02 (2H,bs,NH₂), 4.38-4.07 (4H,m,H5',NHala+CHala), 3.61 (3H,s,OCH₃), 3.54 (3H,d,OCH₃), 3.05-2.52 (5H,m,CH₂aa,H4',CHcPr,+1 of H6'), 1.64-1.52 (1H,m,1 of H6'), 0.77-0.73 (2H,t,J=5.49Hz,2Hof CH₂cPr), 0.51 (2H,bs,2H of CH₂cPr).

35

¹³C NMR: δ 173.3 (CO), 172.4 (CO), 161.5 (C2), 157.7 (C4), 152.3 (C8), 152.1 ('*ipso*'-Ph), 137.8 (C2'), 137.0 (C6), 132.6 (C3'), 131.1 ('*m*'-Ph), 126.4 ('*p*'-Ph), 121.6 ('*o*'-Ph), 116.2 (C5), 70.5 (C5'), 60.3 (C1'), 54.3 (OCH₃), 53.5 (OCH₃), 52.6 (CHala), 47.1 (C4'), 39.7 (CH₂ala), 36.0 (C6'), 25.1 (CHcPr), 8.8 (CH₂cPr).

MS ES⁺: m/z 585.8 (100%, M⁺), 607.7 (30%, M+Na⁺).

40

MS FAB: For C₂₆H₃₃O₅N₇P requires 586.217910, found 586.217510.

HPLC: t_R 29.261 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

IR: 3347.5 (N-Hstr.), 2850.7 (C-Hstr.), 1739.9 (C=Ostr.), 1596.1 (aromatic C-Cstr.), 1461.9 (C-Hdef.), 1376.6 (-CH₃sym. def.), 1262.4 (P=O), 1211.2 (P-O-aryl), 1158.3 (C-Ostr.), 1027.0 (P-O-alkyl), 935.6 (olefinic C-Hdef.), 761.5, 722.0 (monosub.aromatic C-Hdef.).

45

3-cyclohexyl-L-alanine methyl ester hydrochloride salt**C₉H₁₉N₁O₂Cl₁, MW=221.75**

50 [0083] This was synthesised according to **Standard Procedure 1**, using 3-cyclohexyl-L-alanine (3.0g, 17.5mmol), methanol (30ml), and thionyl chloride (2.56ml, 35mmol). The product was isolated as a white solid (3.23g, 83.9%).

¹H NMR (MeOH-d₄): δ 4.12-4.07 (3H,t,CHala), 3.85 (3H,s,OCH₃), 1.74-1.68 (6H,m,CH₂+*o*-CH₂), 1.56-1.43 (1H,m,CH), 1.36-1.15 (4H,m,*m*-CH₂), 1.05-0.90 (2H,q,*p*-CH₂).

¹³C NMR: δ 170.15 (CO), 52.7 (OCH₃), 50.8 (CHala), 38.2 (CH₂), 33.6 (CH), 33.0+32.7 (2xCH₂-*o*), 26.3 (*p*-CH₂), 26.0+25.9 (2xCH₂-*m*).

55

EP 1 117 669 B1

Phenyl-(methoxy-3-cyclohexyl-L-alaninyl)-phosphorochloridate

C₁₈H₂₃N₁O₄P₁Cl₁, MW=359.82

5 [0084] This was synthesised according to **Standard Procedure 3**, using 3-Cyclohexyl-L-alanine methyl ester hydrochloride salt (0.7g, 3.16mmol), PhOP(O)Cl₂ (0.47ml, 3.16mmol), triethylamine (0.88ml, 6.31mmol) in DCM (60ml). The usual workup yielded the crude product as a yellow oil (1.18g, 100%), which was stored in THE (7ml) to give a 0.45M solution.

³¹P NMR: δ 9.79, 9.49 (1:1).

10 ¹H NMR: δ 7.49-7.43 (2H,m,'o'-Ph), 7.37-7.19 (3H,m,'m'+ 'p'-Ph), 4.46-4.35 (1H,q,NHala), 4.32-4.20 (1H,m,CHala), 3.88-3.85 (3H,dd,OCH₃), 1.94-1.90 (1H,d,CHcHx), 1.76-1.60

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-Phenyl-(methoxy-3-cyclohexane-L-alaninyl)-phosphate. Cf1709.

15

C₃₀H₄₀N₇O₅P₁, MW=609.66

[0085] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (150mg, 0.52mmol), tBuMgCl (1.05ml, 1.05mmol, of a 1.0M solution in THF), in THF (4ml) and phenyl-(methoxy-3-cyclohexane-L-alaninyl)-phosphorochloridate (3.5ml, 1.57mmol, of a 0.45M solution in THF), at room temperature for 24hrs. After 24hrs, additional phenyl-(methoxy-3-cyclohexane-L-alaninyl)-phosphorochloridate (2.5ml, 1.12mmol, of a 0.45M solution in THF) was added and the reaction stirred for another 24hrs. The crude product was purified by eluting with 3% MeOH in CHCl₃, and then 2.5% MeOH in CHCl₃ to give the pure product as a pale yellow foamy solid (79.6mg, 24.9%).

25 ³¹P NMR: δ 4.14, 3.98 (1:1).

¹H NMR: δ 7.50 (1H,d,H8), 7.34-7.13 (5H,t,OPh), 6.20 (1H,s,NHcPr), 6.08 (1H,t,H2'), 5.89 (1H,q,H3'), 5.53 (1H,bs,H1'), 5.16 (2H,bs,NH₂), 4.24-3.84 (4H,m,H5',NHala+CHala), 3.66 (3H,s,OCH₃), 3.34 (1H,bs,), 3.11 (1H,d,), 3.03 (1H,bs,), 2.84-2.72 (1H,m,1 of H6'), 1.98-1.36 (8H,m,), 1.11 (3H,bs,), 0.89-0.83 (4H,m,2H of cPr+CH₂'p'), 0.63 (2H,d,2H of cPr).

30 ¹³C NMR: δ 174.8CO 160.2 (C2'), 156.5 (C4), 151.3 (C6), 151.2 ('ipso'-Ph), 136.8 (C2'), 135.9 (C8), 131.5 (C3'), 130.0 ('m'-Ph), 125.2 ('p'-Ph), 120.5 ('o'-Ph), 115.1 (C5), 69.4 (C5'), 59.3 (C1'), 52.7 (CHala), 46.1 (C4'), 42.5 (CH₂), 34.9 (C6'), 33.8 (CHcHx), 32.7 (CH₂'d'), 26.7 (CH₂'m'), 26.4 (CH₂'p'), 24.2 (CHcPr), 7.8 (CH₂cPr).

MS ES⁺: m/z 610.3 (40%, M⁺), 632.3 (100%, M+Na⁺), 633.3 (25%, M+H+Na⁺).

MS FAB: For C₃₀H₄₀O₅N₇NaP requires 632.2726, found 632.2727.

35 HPLC: t_R 42.154 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(L-alaninyl)-phosphate diammonium salt. Cf1540.

40 [0086] (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(methoxy-L-alaninyl)]-phosphate (125mg, 0.24mmol) was stirred in H₂O:NEt₃ (10ml, 1:1 v/v), at 25-35°C for 5hrs. The reaction mixture was extracted with DCM (8x20ml), and the aqueous layer reduced to dryness. The resulting solid was solubilised in isopropanol and purified by flash column chromatography, gradient eluting with i-PrOH:H₂O:NH₃ (11:1:1 to 9:1:2). The appropriate fractions were reduced to dryness and freeze dried to give the pure product as a white foamy solid (106mg, 95%).

45 ³¹P NMR (D₂O): δ 8.62 (s).

¹H NMR (D₂O): δ 7.79 (1H,s,H8), 6.08 (1H,d,H2'), 5.77 (1H,d,H3'), 5.35 (1H,t,H1'), 3.71-3.58 (2H,m,H5'), 3.41-3.32 (1H,m,CHala), 3.02-2.94 (1H,m,NHCH), 2.70-2.59 (2H,m,H4'+1 of CH₂), 1.57-1.49 (1H,dt,1 of CH₂), 1.10 (3H,d,CH₃), 0.83-0.76 (2H,q,1 of CH₂cyclo.), 0.61-0.56 (2H,q,1 of CH₂cyclo.).

50 MS ES⁺: m/z 437.9 (100%, M⁺).

MS FAB: calculated m/z 438.165481, found m/z 438.163790.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(D-alaninyl)-phosphate diammonium salt.

55

[0087] (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(methoxy-D-alaninyl)]-phosphate (100mg, 0.19mmol) was stirred in H₂O:NEt₃ (8ml, 1:1 v/v), for 16hrs. The reaction mixture was extracted with DCM (5x20ml), and the aqueous layer reduced to dryness. The resulting solid was solubilised in iso-

EP 1 117 669 B1

propanol and purified by flash column chromatography, gradient eluting with i-PrOH:H₂O:NH₃ (11:1:1 to 9:1:2). The appropriate fractions were reduced to dryness and freeze dried to give the pure product as a white foamy solid (88%).

³¹P NMR (MeOH-d₄): δ 7.81 (s).

¹H NMR: δ 7.74 (1H, s, H₈), 6.12 (1H, d, J=5.53 Hz, H₂'), 5.78 (1H, t, H₃'), 5.44 (1H, d, J=6.21 Hz, H₁'), 3.74 (2H, t, J=5.42 Hz, H₅'), 3.70-3.60 (1H, m, CHala), 3.01 (1H, bs, H₄'), 2.84 (1H, d, J=3.28 Hz, CHcPr), 2.73-2.63 (1H, dt, J=8.66 Hz+5.17 Hz, 1 of H₆'), 1.67-1.58 (1H, m, 1 of CH₂), 1.21 (3H, d, J=7.01 Hz, CH₃ala), 0.79-0.73 (2H, q, J=6.68 Hz, 2H of CH₂cPr), 0.53 (2H, t, 2H of CH₂cPr).

¹³C NMR: δ 179.8 (CO), 161.2 (C₂), 157.1 (C₄), 151.1 (C₆), 139.5 (C₂'), 137.8 (C₈), 130.7 (C₃'), 114.6 (C₅), 68.0 (C₅'), 60.5 (C₁'), 51.9 (CHala), 47.6 (C₄'), 35.9 (C₆'), 24.4 (CHcPr), 21.7 (CH₃ala), 7.6 (CH₂cPr).

MS ES⁺: m/z 437.9 (100%, M⁺).

MS FAB: calculated m/z 438.165481, found m/z 438.167842.

Phenyl-(ethoxy-L-alaninyl)-phosphorochloridate.

C₁₁H₁₅O₄N₁Cl₁P₁, MW=291.67.

[0088] This was synthesised according to **Standard Procedure 3**, using L-Alanine ethyl ester hydrochloride (1.0g, 6.51mmol), PhOP(O)Cl₂ (1.37g, 0.97ml, 6.51mmol) and NEt₃ (1.32g, 1.81ml, 13.0mmol) to yield 1.85g (97.4%) of crude product as an oil that was stored in anhydrous THF (10ml), to give a 0.63mmol/ml solution that was used without further purification.

³¹P NMR: δ 9.41, 9.16 (1:1).

¹H NMR: δ 7.42-7.35 (2H, dd, 'o'-Ph), 7.31-7.25 (3H, m, 'm'+ 'p'-Ph); 4.71 (1H, d, NHala), 4.31-4.13 (3H, m, OCH₂+CHala), 1.55-1.52 (3H, dd, OCH₂CH₃), 1.33-1.30 (3H, dd, CH₃ala).

¹³C NMR: δ 173.1 (CO), 150.2 ('ipso'-Ph), 130.3 ('m'-Ph), 126.4 ('p'-Ph), 120.9 ('o'-Ph), 62.3 (OCH₂), 51.0 (CHala), 20.9 (CH₂CH₃), 14.5 (CH₃ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(ethoxy-L-alaninyl)]-phosphate. Cf1587.

C₂₄H₃₀O₅N₇P₁, MW=527.53.

[0089] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (300mg, 1.4mmol), tBuMgCl (1.0M solution in THF) (1.57ml, 1.57mmol), and phenyl-(ethoxy-L-alaninyl)-phosphorochloridate (0.49M solution in THF) (6.45ml, 3.14mmol) in anhydrous THF (20ml), and stirring at room temperature for 24hrs. The crude product was purified by column chromatography eluting with 2.5% MeOH in CHCl₃ to give the product as a pale yellow foam (290mg, 51.1%).

³¹P NMR: δ 4.04, 3.96 (1:1).

¹H NMR: δ 7.39 (1H, d, J=7.56 Hz, H₈), 7.23-7.18 (2H, t, J=7.90 Hz, 'o'-Ph), 7.12-7.10 (2H, t, 'm'-Ph), 7.06-7.01 (1H, t, J=7.13 Hz, 'p'-Ph), 6.18 (1H, bs, NHcPr), 5.97-5.95 (1H, t, H₂'), 5.79-5.75 (1H, t, J=5.55 Hz, H₃'), 5.43 (1H, s, H₁'), 5.13 (2H, bs, NH₂), 4.30-4.14 (1H, m, NHala), 4.06-4.00 (4H, m, H₅' + OCH₂), 3.96-3.84 (1H, m, CHala), 3.03 (1H, d, J=5.74 Hz, H₄'), 2.92 (1H, bs, CHcPr), 2.71-2.61 (1H, m, 1 of H₆'), 1.60-1.51 (1H, m, 1 of H₆'), 1.29-1.24 (3H, t, J=6.64 Hz, CH₃ala), 1.18-1.11 (3H, m, CH₂CH₃), 0.75-0.71 (2H, q, J=6.76 Hz, 2H of CH₂cPr), 0.50 (2H, bs, 2H of CH₂cPr).

¹³C NMR: δ 173.35 (CO), 159.8 (C₂), 156.0 (C₄), 150.6 (C₆), 150.4 ('ipso'-Ph), 136.1 (C₂'), 135.1 (C₈), 130.8 (C₃'), 129.3 ('m'-Ph), 124.5 ('p'-Ph), 119.8 ('o'-Ph), 114.4 (C₅), 68.6 (C₅'), 61.2 (OCH₂), 58.5 (C₁'), 50.0 (CHala), 45.3 (C₄'), 34.3 (C₆'), 23.4 (CHcPr), 20.6 (CH₃ala), 13.8 (CH₂CH₃), 7.0 (CH₂cPr).

MS ES⁺: m/z 541.9 (100%, M⁺), 546.84 (28%, M+H⁺), 563.8 (25%, M+Na⁺).

MS FAB: For C₂₅H₃₃O₅N₇P, requires 542.228081, found 542.228131.

HPLC: t_R 31.76, 32.03 (100%)-(100% water (0mins) 20% water (35mins), 20% water (45mins), 100% water (55mins)).

IR: 3334.1 (N-Hstr.), 1734.5 (C=Ostr.), 1595.9, 1488.0 (aromatic C-Cstr.), 1450.3 (C-Hdef.), 1394.2 (-CH₃sym.def.), 1252.8 (P=O), 1210.4 (P-O-aryl), 1153.3 (C-Ostr.), 1026.0 (P-O-alkyl), 934.8 (olefinic C-Hdef.), 759.0 (monosub.aromatic C-Hdef.).

Phenyl-(benzoxy-L-alaninyl)-phosphorochloridate.

C₁₆H₁₇O₄N₁Cl₁P₁, MW=353.74.

[0090] This was synthesised according to **Standard Procedure 3**, using L-alanine benzyl ester hydrochloride (1.0g,

EP 1 117 669 B1

4.64mmol), PhOP(O)Cl₂ (0.98g, 0.69ml, 4.64mmol) and NEt₃ (0.94g, 1.29ml, 9.27mmol) to yield 1.61g (98.2%) of crude product that was stored in anhydrous THF (10ml), to give a 0.46mmol/ml solution that was used without further purification.

³¹P NMR: δ 9.41, 9.23 (1:1).

5 ¹H NMR: δ 7.41-7.21 (10H,m,2xPh), 5.24 (2H,d,CH₂Ph), 4.95-4.88 (1H,t,NHala), 4.36-4.15 (1H,m,CHala), 1.56 (3H,t,CH₃ala).

¹³C NMR: δ 172.9 (CO), 150.2 ('*ipso*'-OPh), 135.5 ('*ipso*'-CH₂Ph), 130.3 ('*m*'-OPh), 129.0 ('*o*'-CH₂Ph), 128.7 ('*m*'-*p*'-CH₂Ph), 126.4 ('*p*'-OPh), 121.0 ('*o*'-OPh), 68.0 (OCH₂), 51.1 (CHala), 20.8 (CH₃ala).

10 **(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(benzoxy-L-alaninyl)]-phosphate. C11582.**

C₃₀H₃₅O₅N₇P₁, MW=603.6.

15 **[0091]** This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (400mg, 1.4mmol), tBuMgCl (1.0M solution in THF) (2.1ml, 2.1mmol), and phenyl-(benzoxy-L-alaninyl)-phosphorochloridate (0.46M solution in THF) (9.2ml, 4.19mmol) in anhydrous THF (20ml), and stirring at room temperature for 64hrs. The crude product was purified by column chromatography eluting with 3% MeOH in CHCl₃, and then 2.5% MeOH in CHCl₃ to give the product as a white foam (82.2mg, 9.75%).

20 A second synthesis was undertaken with (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (200mg, 0.7mmol), tBuMgCl (2.43ml of a 1.0M soln in THF, 2.43mmol), and phenyl-(benzoxy-L-alaninyl)-phosphorochloridate (2.2ml of a 0.46M soln in THF, 2.1mmol) in THF (2.5ml). Purification by column chromatography eluting with 3% MeOH in CHCl₃ gave the pure product as a white foamy solid (90mg, 21.3%).

³¹P NMR: δ 3.82, 3.72 (1:1).

25 ¹H NMR: δ 7.51 (1H,d,H8), 7.37-7.15 (10H,m,OPh+CH₂Ph), 6.10-6.04 (1H,m,H2'), 5.96 (1H,bs,NHcPr), 5.89 (1H,dd, J=5.36Hz,H3'), 5.54 (1H,t,H1'), 5.16 (2H,bs,NH₂), 4.96 (2H,bs,CH₂Ph), 4.23-4.05 (3H,m,NHala+H5'), 3.89-3.70 (1H,dt,CHala), 3.16-3.12 (1H,t,H4'), 3.03 (1H,bs,CHcPr), 2.85-2.71 (1H,m,1of H6'), 1.74-1.64 (1H,m,1of H6'), 1.44-1.39 (3H,t,J=7.84Hz,CH₃ala), 0.88 (2H,q,J=6.75Hz,2H of CH₂cPr), 0.64 (2H,m,2H of CH₂cPr).

30 ¹³C NMR: δ 173.3 (CO), 159.7 (C2), 156.0 (C4), 150.9 (C6), 150.7 ('*ipso*'-OPh), 136.4 (C2'), 135.7 ('*ipso*'-Bn), 135.2 (C8), 131.0 (C3'), 129.6 ('*o*'-Bn), 128.6 ('*m*'-Bn), 128.5 ('*p*'-Bn), 128.2 ('*m*'-OPh), 124.9 ('*p*'-OPh), 120.1 ('*o*'-OPh), 114.8 (C5), 68.8 (C5'), 67.2 (CH₂Ph), 58.9 (C1'), 50.3 (CHala), 45.6 (C4'), 34.4 (C6'), 23.7 (CHcPr), 21.0 (CH₃ala), 7.4 (CH₂cPr).

MS ES⁺ : m/z 603.8 (100%, M⁺), 604.8 (30%, M+H⁺), 625.7 (20%, M+Na⁺).

MS FAB: For C₃₀H₃₅O₅N₇P requires 604.243731, found 604.241775.

35 HPLC: t_R 33.39 (99.7%)-(100% water (0mins) 20% water (35mins), 20% water (45mins), 100% water (55mins)).

IR: 3355.9 (N-Hstr.), 2923.3, 2853.7 (C-Hstr.), 1734.1 (C=Ostr.), 1595.6 (aromatic C-Cstr.), 1458.4 (C-Hdef.), 1376.5 (-CH₃sym.def.), 1154.4 (C-Ostr.), 1028.2 (P-O-alkyl), 935.8 (olefinic C-Hdef.), 721.7 (monosub.aromatic C-Hdef.).

L-Alanine *n*-propyl ester hydrochloride salt.

40

C₆H₁₄N₁O₂Cl₁, MW=167.634

[0092] This was synthesised according to **Standard Procedure 1**, using anhydrous propan-1-ol (42.0ml, 0.56mol), thionyl chloride (8.2ml, 0.112mol) and L-alanine (5.0g, 0.056mol). The product was isolated as a white solid (8.88g, 94.3%).

45 ¹H NMR (MeOH-d₄): δ 4.34-4.26 (2H,m,OCH₂), 4.24-4.17 (1H,q,CHala), 1.88-1.78 (2H,m,CH₂), 1.65 (3H,d,J=7.24Hz, CH₃ala), 1.10-1.05 (3H,t,CH₂CH₃).

¹³C NMR: δ 170.1 (CO), 68.0 (OCH₂), 48.9 (CHala), 21.9 (CH₂), 15.3 (CH₃ala), 9.5 (CH₂CH₃).

50 **Phenyl-(*n*-propoxy-L-alaninyl)-phosphorochloridate**

C₁₂H₁₇N₁O₄P₁Cl₁, MW=305.79

55 **[0093]** This was synthesised according to **Standard Procedure 3**, using L-Alanine *n*-propyl ester hydrochloride salt (0.5g, 2.98mmol), PhOP(O)Cl₂ (0.45ml, 2.98mmol), triethylamine (0.83ml, 5.97mmol) in DCM (70ml). The usual workup yielded the crude product as a yellow oil (0.84g, 92.1%), which was stored in THF (5ml) to give a 0.55M solution.

³¹P NMR: δ 9.41, 9.17 (1:1).

¹³C NMR: δ 173.1 (CO), 150.1 ('*ipso*'-Ph), 130.0 ('*m*'-Ph), 126.4 ('*p*'-Ph), 121.0 ('*o*'-Ph), 67.9 (OCH₂), 51.0 (CHala),

EP 1 117 669 B1

22.3 (CH_2CH_3), 21.0 (CH_3ala), 10.7 (CH_2CH_3).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-Phenyl-(*n*-propoxy-L-alaninyl)-phosphate. Cf1646.

$\text{C}_{26}\text{H}_{34}\text{N}_7\text{O}_5\text{P}_1$, MW=555.57

[0094] This was synthesised according to Standard Procedure 4, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), *t*BuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THE (3ml) and phenyl-(*n*-propyl-L-alaninyl)-phosphorochloridate (1.9ml, 1.05mmol, of a 0.55M solution in THF), at room temperature for 24hrs. The crude product was purified by eluting with 3% MeOH in CHCl_3 to give the pure product as a pale yellow foamy solid (123mg, 63.4%).

^{31}P NMR: δ 4.06, 3.98 (1:1).

^1H NMR: δ 7.40 (1H,d,J=7.99Hz,H8), 7.23-7.18 (2H,dd,'*o*'-Ph), 7.12-7.02 (3H,m,'*m*'+'*p*'-Ph), 6.16 (1H,bs,H3'), 5.96 (1H,t,H2'), 5.78 (1H,d,J=5.83Hz,NHcyc), 5.44 (1H,bs,H1'), 5.15 (2H,bs,NH₂), 4.33-4.18 (1H,m,CHala), 4.15-4.04 (2H,m,OCH₂), 4.01-3.88 (2H,m,H5'), 3.65 (1H,bs,NHala), 3.03 (1H,d,H4'), 2.92 (1H,bs,CHcyc), 2.72-2.62 (1H,m,1 of H6'), 1.60-1.47 (3H,m,1 of H6'+ CH_2CH_3), 1.30-1.26 (3H,t,CH₃ala), 0.84-0.80 (3H,m,CH₂CH₃), 0.73 (2H,d,J=6.8Hz,1 of CH₂cyc), 0.51 (2H,bs, 1 of CH₂cyc).

^{13}C NMR: δ 174.1(CO 160.4 (C2), 156.6 (C4), 151.1 (C6+'*ips*'-Ph), 136.8 (C2'), 135.9 (C8), 131.5 (C3'), 130.0 ('*m*'-Ph), 125.2 ('*p*'-Ph), 120.5 ('*o*'-Ph), 115.0 (C5), 69.2 (C5'), 67.4 (OCH₂), 59.2 (C1'), 50.6 (CHala), 46.0 (C4'), 35.0 (C6'), 24.2 (CHcPr), 22.3 (CH_2CH_3), 21.5 (CH₃ala), 10.7 (CH₂CH₃), 7.7 (CH₂cyc).

MS ES⁺: *m/z* 555.8 (100%, M⁺), 557.0 (30%, M+H⁺).

MS FAB: For $\text{C}_{26}\text{H}_{35}\text{O}_5\text{N}_7\text{P}$ requires 556.2437, found 556.2438.

HPLC: t_R 34.708 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

L-Alanine *n*-butyl ester hydrochloride salt.

$\text{C}_7\text{H}_{16}\text{N}_1\text{O}_2\text{Cl}_1$, MW=181.661

[0095] This was synthesised according to Standard Procedure 1, using anhydrous butan-1-ol (51.4ml, 0.56mol), thionyl chloride (8.2ml, 0.112mol) and L-alanine (5.0g, 0.056mol). The product was isolated as a white solid (8.86g, 86.9%).

^1H NMR (MeOH-*d*₄): δ 4.29-4.17 (2H,m,OCH₂), 4.13-4.06 (1H,q,CHala), 1.71-1.62 (2H,m,OCH₂CH₂), 1.53 (3H,d,J=7.25Hz,CH₃ala), 1.47-1.34 (2H,m,CH₂CH₃), 0.96-0.91 (3H,t,CH₂CH₃).

^{13}C NMR: δ 170.1 (CO), 66.2 (OCH₂), 48.9 (CHala), 30.6 (OCH₂CH₂), 19.0 (CH₂CH₃), 15.3 (CH₃ala), 13.0 (CH₂CH₃).

Phenyl-(*n*-butoxy-L-alaninyl)-phosphorochloridate

$\text{C}_{13}\text{H}_{19}\text{N}_1\text{O}_4\text{P}_1\text{Cl}_1$, MW=317.82

[0096] This was synthesised according to Standard Procedure 3, using L-Alanine *n*-butyl ester hydrochloride salt (0.5g, 2.75mmol), PhOP(O)Cl₂ (0.41ml, 2.75mmol), triethylamine (0.77ml, 5.5mmol) in DCM (80ml). The usual workup yielded the crude product as a yellow oil (0.84g, 94.5%), which was stored in THF (5ml) to give a 0.525M solution.

^{31}P NMR: δ 9.39, 9.10 (1:1).

^1H NMR: δ 7.43-7.15 (5H,m,Ph), 4.68-4.59 (1H,q,CHala), 4.27-4.05 (3H,m,OCH₂+NHala), 1.73-1.59 (2H,m,OCH₂CH₂), 1.56-1.53 (2H,dd,CH₂CH₃), 1.46-1.37 (3H,m,CH₃ala), 1.00-0.92 (3H,m,CH₂CH₃).

^{13}C NMR: δ 173.2 (CO), 150.1 ('*ips*'-Ph), 130.3 ('*m*'-Ph), 126.4 ('*p*'-Ph), 121.0 ('*o*'-Ph), 66.2 (OCH₂), 51.0 (CHala), 30.9 (OCH₂CH₂), 21.0 (CH₃ala), 19.4 (CH₂CH₃), 14.1 (CH₂CH₃).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-Phenyl-(*n*-butoxy-L-alaninyl)-phosphate. Cf1647.

$\text{C}_{27}\text{H}_{38}\text{N}_7\text{O}_5\text{P}_1$, MW=569.597

[0097] This was synthesised according to Standard Procedure 4, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), *t*BuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (3ml) and phenyl-(*n*-butyl-L-alaninyl)-phosphorochloridate (2.0ml, 1.05mmol, of a 0.525M solution in THF), at room temperature for 24hrs. The crude product was purified by eluting with 3% MeOH in CHCl_3 to give the pure product

EP 1 117 669 B1

as a pale yellow foamy solid (157mg, 78.9%).

^{31}P NMR: δ 4.01, 3.95(1:1).

^1H NMR: δ 7.40 (1H,d,J=7.32Hz,H8), 7.23-7.18 (2H,t,'o'-Ph), 7.11 (2H,t,'m'-Ph), 7.04 (1H,t,'p'-Ph), 6.02 (1H,bs,H3'), 5.97 (1H,t,H2'), 5.78 (1H,bs,NHcycl), 5.44 (1H,bs,H1'), 5.06 (2H,bs,NH₂), 4.22-3.88 (6H,m,CHala,OCH₂,H5'+NHala), 3.05 (1H,d,H4'), 2.93 (1H,bs,CHcycl), 2.72-2.62 (1H,m,1 of H6'), 1.61-1.47 (3H,m,1 of H6'+OCH₂CH₂), 1.30-1.26 (5H, t,CH₃ala+CH₂CH₃), 0.85-0.80 (3H,t,CH₂CH₃), 0.74 (2H,d,J=6.45Hz, 1 of CH₂cycl), 0.51 (2H,bs, 1 of CH₂cycl).

^{13}C NMR: δ 174.1(CO), 160.4 (C2), 156.7 (C4), 151.2 (C6), 151.1 ('ipso'-Ph), 136.7 (C2'), 135.8 (C8), 131.5 (C3'), 130.0 ('m'-Ph), 125.2 ('p'-Ph), 120.5 ('o'-Ph), 115.0 (C5), 69.3

(C5'), 65.8 (OCH₂), 59.2 (C1'), 50.6 (CHala), 46.0 (C4'), 35.0 (C6'), 30.9 (OCH₂CH₂), 24.1 (CHcPr), 21.5 (CH₃ala), 19.4 (CH₂CH₃), 14.1 (CH₂CH₃), 7.8 (CH₂cycl).

MS ES⁺: m/z 569.9 (70%, M⁺), 570.9 (20%, M+H⁺), 591.8 (100%, M+Na⁺), 607.8 (20%, M+K⁺).

HPLC: t_R 38.27 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

L-Alanine *i*-propyl ester hydrochloride salt.

$\text{C}_6\text{H}_{14}\text{N}_1\text{O}_2\text{Cl}_1$, MW=167.634

[0098] This was synthesised according to **Standard Procedure 1**, using anhydrous propan-2-ol (43.0ml, 0.56mol), thionyl chloride (8.2ml, 0.112mol) and L-alanine (5.0g, 0.056mol). The product was isolated as a semicrystalline solid (8.86g, 86.9%).

^1H NMR (MeOH-d₄): δ 5.16-5.08 (1H,m,CHala), 4.11-4.04 (1H,q,OCH(Me)₂), 1.55 (3H,d,J=7.21Hz,CH₃ala), 1.34-1.31 (6H,dd,CH(Me)₂).

^{13}C NMR: δ 169.5 (CO), 70.8 (COCH(Me)₂), 48.9 (CHala), 20.8 (CH₃ala), 15.3 (CH(Me)₂).

Phenyl-(*i*-propoxy-L-alaninyl)-phosphorochloridate

$\text{C}_{12}\text{H}_{17}\text{N}_1\text{O}_4\text{P}_1\text{Cl}_1$, MW=305.79

[0099] This was synthesised according to **Standard Procedure 3**, using L-Alanine *i*-propyl ester hydrochloride salt (0.5g, 2.98mmol), PhOP(O)Cl₂ (0.45ml, 2.98mmol), triethylamine (0.83ml, 5.97mmol) in DCM (70ml). The usual workup yielded the crude product as a yellow oil (1.12g, >100%), which was stored in THF (5ml) to give a 0.597M solution.

^{31}P NMR: δ 9.45, 9.17 (1:1).

^{13}C NMR: δ 172.6 (CO), 150.2 ('ipso'-Ph), 130.3 ('m'-Ph), 126.4 ('p'-Ph), 121.0 ('o'-Ph), 70.1 (OCH), 51.1 (CHala), 22.1 (CH(CH₃)₂), 20.9 (CH₃ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-Phenyl-(*i*-propoxy-L-alaninyl)-phosphate. Cf1661.

$\text{C}_{26}\text{H}_{34}\text{N}_7\text{O}_5\text{P}_1$, MW=555.57

[0100] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THE (3ml) and phenyl-(*i*-propyl-L-alaninyl)-phosphorochloridate (1.76ml, 1.05mmol, of a 0.597M solution in THF), at room temperature for 72hrs. The crude product was purified by eluting with 3% MeOH in CHCl₃ (x2) to give the pure product as a pale yellow foamy solid (106.8mg, 54.8%).

^{31}P NMR: δ 4.02, 3.98 (1:1).

^1H NMR: δ 7.41 (1H,d,J=8.12Hz,H8), 7.24-7.19 (2H,m,'o'-Ph), 7.13-7.03 (3H,m,'m'+p'-Ph), 6.37 (1H,bs,,NHcPr), 5.98 (1H,t,H3'), 5.80-5.76 (1H,m,H2'), 5.43 (1H,bs,H1'), 5.21 (2H,bs,NH₂), 4.94-4.86 (1H,m,OCH), 4.15-3.98 (2H,m,H5'), 3.92-3.83 (1H,m,CHala), 3.59 (1H,bs,NHala), 3.06-2.98 (1H,m,H4'), 2.93 (1H,bs,CHcPr), 2.74-2.63 (1H,m,1 of H6'), 1.62-1.53 (1H,m,1 of H6'), 1.34-1.18 (3H,m,CH₃ala), 1.15-1.11 (6H,m,CH(CH₃)₂), 0.79-0.73 (2H,q,2H of CH₂cPr), 0.53 (2H,bs,2H of CH₂cPr).

^{13}C NMR: δ 173.5(CO) 159.8 (C2), 156.2 (C4), 151.1 (C6), 151.0 ('ipso'-Ph), 136.9 (C2'), 136.1 (C8), 131.3 (C3'), 130.0 ('m'-Ph), 125.3 ('p'-Ph), 120.5 ('o'-Ph), 115.0 (C5), 69.6 (C5'), 69.2 (OCH), 59.3 (C1'), 50.7 (CHala), 46.0 (C4'), 34.9 (C6'), 24.2 (CHcPr), 22.0 (CH(CH₃)₂), 21.4 (CH₃ala), 7.8 (CH₂cycl).

ES⁺: m/z 555.9 (100%, M⁺), 556.9 (30%, M+H⁺).

MS MALDI/TOF: For C₂₆H₃₅O₅N₇P found 555.575.

HPLC: t_R 35.85 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

EP 1 117 669 B1

Phenyl-*tert*-butoxy-L-alaninyl phosphorochloridate.

$C_{16}H_{17}O_4N_1Cl_1P_1$, MW=353.74.

- 5 [0101] This was synthesised according to **Standard Procedure 3**, using L-alanine *tert*-butyl ester hydrochloride (0.5g, 2.75mmol), $PhOP(O)Cl_2$ (0.41ml, 2.75mmol) and NEt_3 (0.77ml, 5.5mmol) to yield 0.77g (87.5%) of crude product that was stored in anhydrous THF (5ml), to give a 0.48mmol/ml solution that was used without further purification.
- ^{31}P NMR: δ 9.53, 9.20 (1:1).
- 1H NMR: δ 7.44-7.39 (2H,t,'*o*'-Ph), 7.32-7.26 (3H,m,'*m*'+'*p*'-Ph), 4.47-4.34 (1H,m,NHala), 4.17-4.04 (1H,m,CHala), 1.53 (9H,3s,3xCH₃).
- 10 ^{13}C NMR: δ 170.7 (CO), 148.7 ('*ipso*'-Ph), 128.9 ('*o*'-Ph), 124.9 ('*p*'-Ph), 119.5 ('*m*'-Ph), 81.65 (CMe₃), 50.0 (CHala), 26.9 (3xCH₃).

- 15 (1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl-*tert*-butoxy-L-alaninyl)-phosphate. Cf1645.

$C_{24}H_{30}O_5N_7P_1$, MW=603.6.

- 20 [0102] This was synthesised according to **Standard Procedure 4**, using (1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (140mg, 0.52mmol), $tBuMgCl$ (1.05ml, 1.05mmol of a 1.0M solution in THF), and phenyl-(*tert*-butoxy-L-alaninyl)-phosphorochloridate (3.3ml, 1.57mmol, of a 0.48M solution in THF), in anhydrous THF (4ml) stirring at room temperature for 48hrs. The crude product was purified by eluting with 3% MeOH in $CHCl_3$ to give the pure product as white foamy solid (192.3mg, 69.0%).
- ^{31}P NMR: δ 4.15 (s).
- 25 1H NMR: δ 7.40 (1H,d,J=8.35Hz,H8), 7.23-7.18 (2H,t,'*m*'-Ph), 7.12 (2H,d,'*o*'-Ph), 7.06-7.02 (1H,t,'*p*'-Ph), 6.09 (1H,bs,H2'), 5.97 (1H,bs,H3'), 5.77 (1H,d,NHcPr), 5.44 (1H,bs,H1'), 5.10 (2H,bs,NH₂), 4.14-4.05 (3H,m,H5'+NHala), 3.85-3.77 (1H,q,CHala), 3.04 (1H,bs,H4'), 2.93 (1H,bs,CHcPr), 2.72-2.62 (1H,m,1 of H6'), 1.58-1.53 (1H,t,1 of H6'), 1.34 (9H,d,CMe₃), 1.27-1.23 (3H,t,CH₃ala), 0.73 (2H,d,2Hof CH₂cPr), 0.51 (2H,bs,2Hof CH₂cPr).
- ^{13}C NMR: δ 173.2 (CO), 160.4 (C2), 156.7 (C4), 151.2 (C6+'*ipso*'-Ph), 136.8 (C2'), 135.9 (C8), 131.5 (C3'), 130.0 ('*m*'-Ph), 125.2 ('*p*'-Ph), 120.6 ('*o*'-Ph), 115.2 (C5), 82.3 (C[CH₃]₃), 69.3 (C5'), 59.1 (C1'), 46.0 (C4'), 35.0 (C6'), 28.3 (3xCH₃), 24.2 (CHcPr), 21.5 (CH₃ala), 7.8 (CH₂cPr).
- 30 MS ES⁺: m/z 570.0 (100%, M⁺), 570.9 (32%, M+H⁺).
- MS FAB: For $C_{27}H_{37}O_5N_7P$ requires 570.2594, found 570.2598.
- HPLC: t_R 36.158 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

35

L-Alanine *n*-pentyl ester hydrochloride salt

$C_8H_{16}N_1O_2Cl_1$, MW=195.69

- 40 [0103] This was synthesised according to **Standard Procedure 1**, using pentan-1-ol (36.3ml, 0.337mol), thionyl chloride (4.92ml, 67.4mmol) and L-Alanine (3.0g, 33.7mmol). The product was isolated as a white solid pure product (4.86g, 73.7%).
- 1H NMR (MeOH- d_4): δ 4.32-4.20 (2H,m,OCH₂), 4.16-4.08 (1H,m,CHala), 1.77-1.68 (2H,m,OCH₂CH₂), 1.56 (3H,d,J=7.22Hz,CH₃ala), 1.42-1.36 (4H,m,CH₂CH₂CH₃), 0.97-0.93 (3H,m,CH₂CH₃).
- 45 ^{13}C NMR: δ 170.1 (CO), 66.5 (OCH₂), 48.8 (CHala), 28.2 (OCH₂CH₂), 28.0 (CH₂CH₂CH₃), 22.3 (CH₂CH₃), 15.2 (CH₃ala), 13.3 (CH₂CH₃).

Phenyl-(*n*-pentoxy-L-alaninyl)-phosphorochloridate

- 50 $C_{14}H_{21}N_1O_4P_1Cl_1$, MW=333.78

- [0104] This was synthesised according to **Standard Procedure 3**, using L-Alanine *n*-pentyl ester hydrochloride salt (0.5g, 2.56mmol), $PhOP(O)Cl_2$ (0.38ml, 2.56mmol), triethylamine (0.71ml, 5.11mmol) in DCM (60ml). The usual workup yielded the crude product as a yellow oil (0.79g, 92.6%), which was stored in THF (5ml) to give a 0.47M solution.
- 55 ^{31}P NMR: δ 9.39, 9.12 (1:1).
- 1H NMR: δ 7.43-7.38 (2H,m,'*o*'-Ph), 7.32-7.25 (3H,m,'*m*'+'*p*'-Ph), 4.63 (1H,bd,NHala), 4.24-4.11 (3H,m,OCH₂+CHala), 1.73-1.65 (2H,m,OCH₂CH₂), 1.57-1.53 (3H,dd,CH₃ala), 1.42-1.35 (4H,m,2xCH₂), 0.97-0.91 (3H,m,CH₂CH₃).
- ^{13}C NMR: δ 173.1 (CO), 150.1 ('*ipso*'-Ph), 130.3 ('*m*'-Ph), 126.4 ('*p*'-Ph), 121.0 ('*o*'-Ph), 66.5 (OCH₂), 51.0 (CHala),

EP 1 117 669 B1

28.6 (CH₂-C2), 28.3 (CH₂-C3), 22.7 (CH₂-C4), 21.0 (CH₃ala), 14.1 (CH₃-C5).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-Phenyl-(*n*-pentyloxy-L-alaninyl)-phosphate. Cf1706.

C₂₈H₃₈N₇O₅P₁, MW=583.7

[0105] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (3ml) and phenyl-(*n*-pentyl-L-alaninyl)-phosphorochloridate (2.22ml, 1.05mmol, of a 0.47M solution in THF), at room temperature for 24hrs. The crude product was purified by eluting with 2.5-3.0% MeOH in CHCl₃ (x2) to give the pure product as a pale yellow foamy solid (143.2mg, 70.2%).

³¹P NMR: δ 3.99, 3.95 (1:1).

¹H NMR: δ 7.41 (1H,d,J=7.18Hz,H8), 7.24-7.19 (2H,m,'o'-Ph), 7.12-7.02 (3H,m,'m'+*p'*-Ph), 6.09 (1H,bs,NHcPr), 5.98 (1H,d,H2'), 5.79 (1H,bs,H3'), 5.44 (1H,bs,H1'), 5.09 (2H,bs,NH₂), 4.16-3.88 (6H,m,CHala,OCH₂,H5'+NHala), 3.05 (1H,bs,H4'), 2.94 (1H,bs,CHcPr), 2.73-2.63 (1H,m,1of H6'), 1.62-1.51 (3H,m,1of H6'+OCH₂CH₂), 1.31-1.21 (7H,t,CH₃ala+2xCH₂), 0.81-0.74 (5H,m,CH₃+2Hof CH₂cPr), 0.52 (2H,bs,2Hof CH₂cPr).

¹³C NMR: δ 174.1(CO), 160.1 (C2), 156.5 (C4), 151.2 (C6), 151.1 ('*ipso*'-Ph), 136.8 (C2'), 136.1 (C8), 131.5 (C3'), 130.0 ('*m*'-Ph), 125.2 ('*p'*'-Ph), 120.5 ('*o'*'-Ph), 115.1 (C5), 69.3 (C5'), 66.1 (OCH₂), 59.3 (C1'), 50.7 (CHala), 46.0 (C4'), 34.9 (C6'), 28.6 (CH₂-C2), 28.3 (CH₂-C3), 24.2 (CHcPr), 22.6 (CH₂-C4), 21.5 (CH₃ala), 14.3 (CH₃-C5), 7.8 (CH₂cPr).

MS ES⁺: m/z 584.2 (100%, M⁺), 585.2 (25%, M+H⁺).

MS FAB: For C₂₈H₃₈O₅N₇P requires 584.2750, found 584.2757.

HPLC: t_R 40.294 (99.3%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

L-Alanine *n*-hexyl ester hydrochloride salt

C₈H₂₀N₁O₂Cl₁, MW=209.75

[0106] This was synthesised according to **Standard Procedure 2**, using L-Alanine (2.0g, 22.5mmol), hexan-1-ol (2.82ml, 22.5mmol), *p*-toluene sulfonic acid monohydrate (4.7g, 24.7mmol), and toluene (100ml). L-alanine *n*-hexyl ester hydrochloride was isolated as a white powdery solid (3.32g, 70.5%).

¹H NMR (MeOH-d₄): δ 4.31-4.18 (2H,m,OCH₂), 4.17-4.09 (1H,q,CHala), 1.75-1.66 (2H,m,OCH₂CH₂), 1.57 (3H,d,J=7.20Hz,CH₃ala), 1.45-1.35 (6H,m,[CH₂]₃CH₃), 0.94-0.89 (3H,t,CH₂CH₃).

¹³C NMR: δ 170.1 (CO), 66.5 (OCH₂), 48.9 (CHala), 31.6 (OCH₂CH₂), 28.6 (O[CH₂]₂CH₂), 25.6 (CH₂CH₂CH₃), 22.6 (CH₂CH₃), 15.4 (CH₃ala), 13.4 (CH₂CH₃).

Phenyl-(*n*-hexyloxy-L-alaninyl)-phosphorochloridate

C₁₅H₂₃N₁O₄P₁Cl₁, MW=347.81

[0107] This was synthesised according to **Standard Procedure 3**, using L-Alanine *n*-hexyl ester hydrochloride salt (0.5g, 2.38mmol), PhOP(O)Cl₂ (0.36ml, 2.38mmol), triethylamine (0.66ml, 4.77mmol) in DCM (60ml). The usual workup yielded the crude product as a yellow oil (0.69g, 83.2%), which was stored in THE (4ml) to give a 0.496M solution.

³¹P NMR: δ 9.40, 9.10 (1:1).

¹H NMR: δ 7.44-7.14 (5H,m,OPh), 4.25 (1H,bs,NHala), 4.23-4.03 (3H,m,OCH₂+CHala),

1.70-1.63 (2H,m,CH₂-2), 1.57-1.54 (2H,m,CH₂-3), 1.47-1.32 (7H,m,CH₃ala+2CH₂-4,5), 0.93-0.91 (3H,dd,CH₃-6).

¹³C NMR: δ 173.2 (CO), 150.1 ('*ipso*'-Ph), 130.3 ('*m*'-Ph), 126.4 ('*p'*'-Ph), 120.9 ('*o'*'-Ph), 66.4 (OCH₂), 51.0 (CHala), 31.7 (CH₂-C2), 28.9 (CH₂-C3), 25.8 (CH₂-C4), 22.9 (CH₂-C5), 21.0 (CH₃ala), 14.4 (CH₃-C6).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-Phenyl-(*n*-hexyloxy-L-alaninyl)-phosphate.

C₂₉H₄₀N₇O₅P₁, MW=597.651

[0108] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (3ml) and phenyl-(*n*-hexoxy-L-alaninyl)-phosphorochloridate (2.11ml, 1.05mmol, of a 0.496M solution in THE), at room temperature for 24hrs. Additional phenyl-(*n*-hexoxy-L-alaninyl)-phosphorochloridate (1.5ml, 0.68mmol, of a

EP 1 117 669 B1

0.496M solution in THF), was added and the reaction stirred for a further 24hrs. The crude product was purified by eluting with 3.0% MeOH in CHCl_3 (x2) to give the pure product as a pale yellow foamy solid.

^{31}P NMR: δ 3.94, 3.91 (1:1).

^1H NMR: δ 7.52 (1H,d,J=8.00Hz,H8), 7.36-7.31 (2H,m,'o'-Ph), 7.25-7.15 (3H,m,'m'+p'-Ph), 6.26 (1H,bs,NHcPr), 6.13-6.08 (1H,m,H2'), 5.93-5.88 (1H,m,H3'), 5.58-5.53 (1H,m,H1'), 5.14 (2H,bs,NH2), 4.28-3.89 (6H,m,CHala,OCH2,H5'+NHala), 3.17 (1H,t,H4'), 3.04 (1H,bs,CHcPr), 2.87-2.75 (1H,m,lof H6'), 1.74-1.61 (3H,m,1 of H6'+OCH2CH2), 1.43-1.31 (9H,t,CH3ala+3xCH2), 0.92-0.85 (5H,m,CH3+2Hof CH2cPr), 0.68-0.63 (2H,q,2Hof CH2cPr).
 ^{13}C NMR: δ 174.1(CO), 160.1 (C2), 156.5 (C4), 151.2 (C6), 151.1 ('ipso'-Ph), 136.9 (C2'), 136.0 (C8), 131.4 (C3'), 130.0 ('m'-Ph), 125.3 ('p'-Ph), 120.5 ('o'-Ph), 115.0 (C5), 69.2 (C5'), 66.1 (OCH2), 59.3 (C1'), 50.7 (CHala), 46.0 (C4'), 34.9 (C6'), 31.7 (OCH2CH2), 28.8 (CH2-ester), 25.8 (CH2-ester), 24.2 (CHcPr), 21.9 (CH2-ester), 21.5 (CH3ala), 14.4 (CH3-ester), 7.8 (CH2cPr).

L-Alanine cyclohexyl ester hydrochloride salt

$\text{C}_9\text{H}_{16}\text{N}_1\text{O}_2\text{Cl}_1$, MW=205.71

[0109] This was synthesised according to **Standard Procedure 2**, using L-Alanine (2.0g, 22.5mmol), cyclohexanol (2.34ml, 22.5mmol), *p*-toluene sulfonic acid monohydrate (4.7g, 24.7mmol), and toluene (100ml). The *p*-toluene sulfonate salt was isolated as a pale orange solid (1.45g).

[0110] The reaction was repeated using L-Alanine (3.0g, 33.7mmol), cyclohexanol (5.26ml, 50.6mmol), *p*-toluene sulfonic acid monohydrate (9.62g, 50.6mmol), and toluene (100ml). L-alanine cyclohexyl ester hydrochloride salt was isolated as a white solid (3.15g, 45.45%).

^1H NMR (MeOH- d_4): δ 4.90 (1H,m,OCH), 4.12-4.04 (1H,q,CHala), 1.92-1.81 (2H,m,OCHCH2), 1.80-1.63 (2H,m,OCHCH2), 1.55 (3H,d,J=7.23Hz,CH3ala), 1.49-1.33 (6H,m,[CH2]3).

^{13}C NMR: δ 169.5 (CO), 75.4 (OCH), 48.9 (CHala), 31.3 (2xCH2-o), 25.2 (2xCH2-m), 23.5 (p-CH2), 15.3 (CH3ala).

Phenyl-(c-hexyloxy-L-alaninyl)-phosphorochloridate

$\text{C}_{15}\text{H}_{21}\text{N}_1\text{O}_4\text{P}_1\text{Cl}_1$, MW=345.79

[0111] This was synthesised according to **Standard Procedure 3**, using L-Alanine c-hexyl ester hydrochloride salt (0.7g, 3.4mmol), PhOP(O)Cl2 (0.51ml, 3.4mmol), triethylamine (0.95ml, 6.8mmol) in DCM (60ml). The usual workup yielded the crude product as a yellow oil (1.12g, 95.2%), which was stored in THF (7ml) to give a 0.46M solution.

^{31}P NMR: δ 9.43, 9.07 (1:1).

^1H NMR: δ 7.44-7.33(2H,m,'o'-Ph), 7.32-7.20 (3H,m,'m'+p'-Ph), 4.92-4.83 (1H,m,OCH), 4.55-4.42 (1H,m,NHala), 4.28-4.15 (1H,m,CHala), 1.89 (2H,bd,CH2-'o'), 1.76 (1H,bd,CH2-'o'), 1.54 (3H,d,CH3ala), 1.49-1.32 (6H,m,CH3CH2-'m'+p').

^{13}C NMR: δ 172.5 (CO), 150.1 ('ipso'-Ph), 130.3 ('m'-Ph), 126.4 ('p'-Ph), 121.0 ('o'-Ph), 74.9 (OCH), 51.1 (CHala), 31.8 (CH2-'o'), 25.6 (CH2-'p'), 21.0 (CH3ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-Phenyl-(c-hexyloxy-L-alaninyl)-phosphate. Cf1707.

$\text{C}_{29}\text{H}_{38}\text{N}_7\text{O}_5\text{P}_1$, MW=595.635

[0112] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (3ml) and phenyl-(c-hexoxy-L-alaninyl)-phosphorochloridate (2.28ml, 1.05mmol, of a 0.46M solution in THF), at room temperature for 24hrs. The crude product was purified by eluting with 3-4% MeOH in CHCl_3 , and then 2.5-3.0% MeOH in CHCl_3 to give the pure product as a pale yellow foamy solid (199mg, 95.7%).

^{31}P NMR: δ 4.06, 3.99 (1:1).

^1H NMR: δ 7.42 (1H,d,J=8.15Hz,H8), 7.23-7.18 (2H,m,'o'-Ph), 7.12-7.02 (3H,m,'m'+p'-Ph), 6.31 (1H,bs,NHcPr), 5.98 (1H,bs,H2'), 5.78 (1H,bs,H3'), 5.43 (1H,bs,H1'), 5.21 (2H,bs,NH2), 4.66 (1H,bs,OCH), 4.17-4.02 (3H,m,H5'+NHala), 3.95-3.85 (1H,m,CHala), 3.05-2.94 (2H,m,H4'+CHcPr), 2.73-2.63 (1H,m,lof H6'), 1.69 (2H,bs,CH2-'o'), 1.62-1.53 (2H,m,CH2-'o'), 1.45-1.18 (9H,m,CH3ala+3xCH2-'m'+p'), 0.76 (2H,d,2Hof CH2cPr), 0.53 (2H,bs,2Hof CH2cPr).

^{13}C NMR: δ 172.0(CO), 158.4 (C2), 154.8 (C4), 149.7 (C6), 149.6 ('ipso'-Ph), 135.5 (C2'), 134.7 (C8), 130.0 (C3'), 128.6 ('m'-Ph), 123.8 ('p'-Ph), 119.1 ('o'-Ph), 113.1 (C5), 72.9 (OCH), 67.8 (C5'), 57.9 (C1'), 59.4 (CHala), 44.7 (C4'), 34.5 (C6'), 30.3 (CH2-'o'), 24.2 (CH2-'m'), 22.8 (CHcPr), 22.5 (CH2-'p'), 20.1 (CH3ala), 6.4 (CH2cPr).

EP 1 117 669 B1

MS ES⁺: m/z 596.2 (100%, M⁺), 597.3 (20%, M+H⁺).

MS FAB: For C₂₉H₃₉O₅N₇P requires 596.2750, found 596.2750.

HPLC: t_R 40.502 (99.8%)-(100% water (0mins) 20% water (35mins), 20% water (45mins), 100% water (55mins)).

5 **L-alanine cyclohexane-methyl ester hydrochloride**

C₁₀H₂₀N₁O₂Cl₁, MW=221.75

10 [0113] This was synthesised according to **Standard Procedure 2**, using L-Alanine (3.0g, 33.7 mmol), cyclohexane methanol (4.15ml, 33.7mmol), *p*-toluene sulfonic acid monohydrate (7.05g, 37.1mmol), and toluene (100ml). 9.2g of the the PTSA salt was solubilised in DCM (50ml), and washed with 10% K₂CO₃ (50ml), and water (2x50ml), dried over MgSO₄, filtered and the filtrate reduced to dryness to give a yellow oil. This was neutralised with 2M HCl, stirred for 2hrs, and then freeze-dried to give the hydrochloride salt as a white solid (4.32g, 75.8%).

15 ¹H NMR (MeOH-d₄): δ 4.19-4.01 (3H,m,OCH+CHala), 1.79-1.69 (5H,m,CH+*o*-CH₂), 1.58 (3H,d,J=7.21Hz,CH₃ala), 1.37-1.20 (4H,m,*m*-CH₂), 1.09-0.98 (2H,q,*p*-CH₂).

¹³C NMR: δ 170.1 (CO), 71.3 (OCH₂), 48.9 (CHala), 37.3 (CH), 29.5 (2xCH₂-*o*), 26.4 (*p*-CH₂), 25.7 (2xCH₂-*m*), 15.4 (CH₃ala).

20 **Phenyl-(cyclohexane-methoxy-L-alaninyl)-phosphorochloridate**

C₁₈H₂₃N₁O₄P₁Cl₁, MW=359.82

25 [0114] This was synthesised according to **Standard Procedure 3**, using L-Alanine cyclohexane-methyl ester hydrochloride salt (0.7g, 3.16mmol), PhOP(O)Cl₂ (0.47ml, 3.16mmol), triethylamine (0.88ml, 6.31mmol) in DCM (70ml). The usual workup yielded the crude product as a yellow oil (1.10g, 96.8%), which was stored in THF (6ml) to give a 0.51M solution.

³¹P NMR: δ 9.35, 9.05 (1:1).

¹H NMR: δ 4.61-4.50 (1H,q,NHala), 4.28-4.13 (1H,m,CHala), 4.04-4.00 (2H,q,OCH₂), 1.78-1.74 (7H,t,CHcHx+*o*'-CH₂), 1.57-1.54 (3H,dd,CH₃ala), 1.06-0.96 (2H,q,*p*'-CH₂).

30 ¹³C NMR: δ 173.1 (CO), 150.1 (*ipso*'-Ph), 130.3 (*m*'-Ph), 126.4 (*p*'-Ph), 121.0 (*o*'-Ph), 71.4 (OCH₂), 51.0 (CHala), 37.4 (CHcHx), 29.9 (CH₂'-*o*'), 26.7 (CH₂'-*m*'), 25.9 (CH₂'-*p*'), 21.1 (CH₃ala).

35 **(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-Phenyl-(cyclohexane-methoxy-L-alaninyl)-phosphate. Cf1708.**

C₃₀H₄₀N₇O₅P₁, MW=609.66

40 [0115] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (5ml) and phenyl-(cyclohexane-methoxy-L-alaninyl)-phosphorochloridate (2.06ml, 1.05mmol, of a 0.51M solution in THF), at room temperature for 48hrs. The crude product was purified by eluting with 4-6% MeOH in DCM, and then 3% MeOH in CHCl₃ to give the pure product as a pale yellow foamy solid (161.1mg, 75.6%).

³¹P NMR: δ 3.99, 3.92 (1:1).

45 ¹H NMR: δ 7.40 (1H,d,J=7.07Hz,H8), 7.24-7.19 (2H,t,*o*'-Ph), 7.13-7.03 (3H,m,*m*'+*p*'-Ph), 6.00-5.96 (2H,m,H2'+NH-cPr), 5.79 (1H,q,H3'), 5.45 (1H,d,H1'), 5.05 (2H,bs,NH₂), 4.16-4.01 (3H,m,OCH₂+NHala), 3.98-3.88 (1H,m,CHala), 3.86-3.74 (2H,m,H5'), 3.07-3.00 (1H,t,H4'), 2.94 (1H,bs,CHcPr), 2.74-2.63 (1H,m,lof H6'), 1.88-1.50 (7H,m,CH-cHx+2CH₂'-*o*'), 1.31-1.27 (3H,t,CH₃ala), 1.21-0.99 (4H,m,2CH₂'-*m*'), 0.89-0.79 (2H,q,CH₂'-*p*'), 0.75 (2H,d,2Hof CH₂cPr), 0.54-0.50 (2H,t,2Hof CH₂cPr).

50 ¹³C NMR: δ 174.1(CO), 160.2 (C2), 156.4 (C4), 151.2 (C6), 151.1 (*ipso*'-Ph), 136.7 (C2'), 136.0 (C8), 131.5 (C3'), 130.0 (*m*'-Ph), 125.2 (*p*'-Ph), 120.5 (*o*'-Ph), 115.1 (C5), 71.0 (OCH₂), 69.3 (C5'), 59.3 (C1'), 50.7 (CHala), 46.1 (C4'), 37.4 (CHcHx), 34.9 (C6'), 29.9 (CH₂'-*o*'), 26.6 (CH₂'-*m*'), 25.9 (CH₂'-*p*'), 24.2 (CHcPr), 21.5 (CH₃ala), 7.8 (CH₂cPr).

MS ES⁺: m/z 610.3 (50%, M+H⁺), 632.3 (100%, M+Na⁺), 633.3 (M+H+Na⁺).

MS FAB: For C₃₀H₄₀O₅N₇NaP requires 632.2726, found 632.2710.

HPLC: t_R 42.859 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

55

EP 1 117 669 B1

4-Chlorophenyl-phosphorodichloridate



5 [0116] Phosphorus oxychloride (2ml, 21.5mmol) was stirred with anhydrous diethylether (70ml) in a 250ml RBF. To this was added, dropwise, a solution of 4-chlorophenol (2.1ml, 21.5mmol), and anhydrous triethylamine (3.0ml, 21.5mmol) in anhydrous diethylether (30ml) at -80°C. This was stirred vigorously at -80°C for 1hr and left to rise to room temperature over 16hrs. The triethylamine hydrochloride salt was filtered off, and the filtrate reduced to dryness to give the crude product as a yellow oil (4.61 g, 87.2%).

10 ^{31}P NMR: δ 4.99 (s).

^{13}C NMR: δ 148.4 ('*ipso*'-Ph), 133.2 ('*p*'-Ph), 130.7 ('*m*'-Ph), 122.4 ('*o*'-Ph).

4-Chlorophenyl-(methoxy-L-alaninyl)-phosphorochloridate



[0117] This was synthesised according to Standard Procedure 3, using L-Alanine methyl ester hydrochloride (2.61g, 18.7mmol) and *p*-chlorophenyl phosphorodichloridate (4.61g, 18.7mmol) and triethylamine (5.21ml, 37.4mmol) in anhydrous DCM (100ml). The usual workup yielded the crude product as a colourless crude oil (3.76g, 64.4%) which was stored in anhydrous THF (20ml) to give a 0.6M solution that was used without further purification.

20 ^{31}P NMR: δ 9.48, 9.25 (1:1).

^1H NMR: δ 7.36 (2H,d,J=8.20Hz,'*o*'-Ph), 7.32-7.22 (2H,m,'*m*'-Ph), 4.69 (1H,d,NHala), 4.27-4.15 (1H,m,CHala), 3.82 (3H,d,OCH₃), 1.56-1.53 (3H,dd,J=7.04Hz,CH₃ala).

25 ^{13}C NMR: δ 173.4 (CO), 148.6 ('*ipso*'-Ph), 131.9 ('*p*'-Ph), 130.3 ('*m*'-Ph), 122.3 ('*o*'-Ph), 53.2 (OCH₃), 50.9 (CHala), 20.9 (CH₃ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
O-[4-chlorophenyl-(methoxy-L-alaninyl)]-phosphate. Cf1620.

[0118] This was synthesised according to Standard Procedure 4, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (250mg, 0.87mmol), tBuMgCl (1.75ml, 1.75mmol of a 1.0M solution in THF), and 4-chlorophenyl-(methoxy-L-alaninyl)-phosphorochloridate (4.37ml, 2.62mmol, of a 0.6M solution in THF), in anhydrous THF (13ml) stirring at room temperature for 24hrs. The crude product was purified by eluting with 3% MeOH in CHCl₃ to give the pure product as white foamy solid (364.5mg, 74.5%).

35 ^{31}P NMR: δ 4.01 (s).

40 ^1H NMR: δ 7.42 (1H,d,H8), 7.22-7.17 (2H,m,'*m*'-Ph), 7.09-7.03 (2H,t,'*o*'-Ph), 5.99 (1H,d,H2'), 5.93 (1H,s,H3'), 5.83 (1H,bs,NHcPr), 5.45 (1H,bs,H1'), 4.96 (2H,bs,NH₂), 4.11 (2H,bs,H5'), 4.03-3.86 (1H,m,CHala), 3.62 (3H,s,OCH₃), 3.07 (1H,d,J=5.9Hz,H4'), 2.92 (1H,bs,CHcPr), 2.76-2.64 (1H,m,lof H6'), 1.64-1.59 (1H,t,1 of H6'), 1.32-1.26 (3H,q,CH₃ala), 0.76 (2H,d,J=6.40Hz,2H of CH₂cPr), 0.53 (2H,bs,2H of CH₂cPr).

^{13}C NMR: δ 174.4 (CO), 160.4 (C2), 156.7 (C4), 151.3 (C6), 149.7 ('*ipso*'-Ph), 136.7 (C2'), 135.9 (C8), 131.6 (C3'), 130.5 ('*p*'-Ph), 130.0 ('*m*'-Ph), 121.9 ('*o*'-Ph), 115.2 (C5), 69.4 (C5'), 59.25 (C1'), 52.9(OCH₃), 50.6 (CHala), 46.0 (C4'), 34.9 (C6'), 24.1 (CHcPr), 21.4 (CH₃ala), 7.8 (CH₂cPr).

45 HPLC: t_R 32.693, 33.012 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

4-Bromophenyl-phosphorodichloridate



[0119] This was synthesised by a method analogous to that of 4-chlorophenylphosphorodichloridate, except using: Phosphorus oxychloride (3.29g, 2ml, 21.5mmol), and 4-bromophenol (3.71g, 21.5mmol) in anhydrous diethylether (70ml), and anhydrous triethylamine (2.71g, 3ml, 21.5mmol) in anhydrous diethylether (30ml). The reaction was stirred at -80°C to room temperature for 16hrs. After filtration, and removal of the solvent, the product was obtained as a clear liquid (5.14g, 82.6%).

^{31}P NMR: δ 4.88 (s).

^1H NMR: δ 7.63 (2H,d,J=8.14Hz,'*o*'-Ph), 7.28 (2H,t,'*m*'-Ph),

EP 1 117 669 B1

^{13}C NMR: δ 149.0 ('*ipso*'-Ph), 133.7 ('*m*'-Ph), 122.6 ('*d*'-Ph), 120.9 ('*p*'-Ph).

4-Bromophenyl-(methoxy-L-alaninyl)-phosphorochloridate

5 **C₁₀H₁₂N₁O₄P₁Cl₁Br₁, MW=356.55**

[0120] This was synthesised according to **Standard Procedure 3**, using L-alanine methyl ester hydrochloride salt (1.0g, 7.16mmol), 4-bromophenyl-phosphorodichloridate (1.82g, 7.16mmol), triethylamine (2ml, 14.3mmol) in DCM (70ml). The usual workup yielded the crude product as a yellow oil (2.24g, 87.7%), which was stored in THF (12ml) to
10 give a 0.524M solution.

^{31}P NMR: δ 9.16, 9.10 (1:1).

^{13}C NMR: δ 173.4(CO), 150.1 ('*ipso*'-Ph), 133.3 ('*m*'-Ph), 122.7 ('*d*'-Ph), 119.6 ('*p*'-Ph), 53.3 (OCH₃), 51.0 (CHala), 20.9 (CH₃ala).

15 **(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
O-[4-bromophenyl-(methoxy-L-alaninyl)]-phosphate. Cf1710.**

C₂₄H₂₉N₇O₅P₁Br₁, MW=606.42

20 [0121] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (5ml) and 4-bromophenyl-(methoxy-L-alaninyl)-phosphorochloridate (2.0ml, 1.05mmol, of a 0.524M solution in THF), at room temperature for 24hrs. The crude product was purified by eluting with 4-6% MeOH in DCM, and then in
25 4% MeOH in DCM, to give the pure product as a white foamy solid (115.2mg, 54.4%).

^{31}P NMR: δ 3.96 (s).

^1H NMR: δ 7.42 (1H,d,H8), 7.34-7.30 (2H,dd,J=8.73Hz,'*o*'-Ph), 7.03-6.97 (2H,t,J=8.68Hz,'*m*'-Ph), 6.02-5.97 (2H,m,H2'+NHcPr), 5.83-5.79 (1H,m,H3'), 5.43 (1H,t,H1'), 5.06 (2H,bs,NH₂), 4.28-4.04 (3H,m,H5'+NHala), 4.02-3.85 (1H,m,CHala), 3.61 (3H,d,OCH₂), 3.05 (1H,d,J=6.09Hz,H4'), 2.94 (1H,d,CHcPr), 2.75-2.66 (1H,m,lof H6'), 1.66-1.56 (1H,m,1 of H6'), 1.31-1.25 (3H,dd,CH₃ala), 0.79-0.72 (2H,q,2Hof CH₂cPr), 0.54-0.49 (2H,t,2Hof CH₂cPr).

30 ^{13}C NMR: δ 174.4(CO), 160.3 (C2), 156.6 (C4), 151.3 (C6) 150.2 ('*ipso*'-Ph), 136.7 (C2'), 136.0 (C8), 133.0 ('*m*'-Ph), 131.6 (C3'), 122.4 ('*d*'-Ph), 118.1 ('*p*'-Ph), 115.2 (C5), 69.4 (C5'), 59.3 (C1'), 52.9 (OCH₃), 50.6 (CHala), 46.0 (C4'), 34.8 (C6'), 24.2 (CHcPr), 21.3 (CH₃ala), 7.8 (CH₂cPr).

MS ES⁺: m/z 606.13 (40%, M⁺), 628.1065 (100%, 79-M+Na⁺), 630.0967 (95%, 81-M+Na⁺).

MS FAB: For C₂₄H₂₉O₅N₇NaPBr requires 628.1049, found 628.1058, and C₂₄H₂₉O₅N₇NaP ⁸¹ Br requires 630.1028,
35 found 630.1042.

HPLC: t_R 35.882 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

4-Fluorophenyl-phosphorodichloridate

40 **C₆H₄O₂P₁Cl₂F₁, MW=228.97**

[0122] This was synthesised by a method analogous to that of 4-chlorophenylphosphorodichloridate, except using: Phosphorus oxychloride (3.29g, 2ml, 21.5mmol), and 4-fluorophenol (2.41g, 21.5mmol) in anhydrous diethylether (70ml), and anhydrous triethylamine (2.71g, 3ml, 21.5mmol) in anhydrous diethylether (30ml). The reaction was stirred
45 at -80°C for 4hrs, and then at room temperature for 2hrs. After filtration, and removal of the solvent, the product was obtained as a clear liquid (4.08g, 83.0%).

^{31}P NMR: δ 5.50 (s).

^1H NMR: δ 7.29-7.24 (2H,m,'*d*'-Ph), 7.09 (2H,t,J=8.29Hz,'*m*'-Ph),

^{13}C NMR: δ 159.7 ('*ipso*'-Ph), 145.8 ('*m*'-Ph), 122.6 ('*d*'-Ph), 117.5 ('*p*'-Ph).

50

4-Fluorophenyl-(methoxy-L-alaninyl)-phosphorochloridate

C₁₀H₁₂N₁O₄P₁Cl₁F₁, MW=295.65

55 [0123] This was synthesised according to **Standard Procedure 3**, using L-alanine methyl ester hydrochloride salt (1.0g, 7.16mmol), 4-fluorophenyl-phosphorodichloridate (1.64g, 7.16mmol), triethylamine (2ml, 14.3mmol) in DCM (70ml). The usual workup yielded the crude product as a yellow oil (1.97g, 93.0%), which was stored in THF (12ml) to give a 0.56M solution.

EP 1 117 669 B1

³¹P NMR: δ 9.84, 9.60(1:1).

¹H NMR: δ 7.32-7.23(2H,m,'*o*'-Ph), 7.12-7.06 (2H,m,'*m*'-Ph), 4.69 (1H,bs,NHala), 4.22 (1H,bs,CHala), 3.82 (3H,d, OCH₃), 1.57-1.53 (3H,m,CH₃ala).

¹³C NMR: δ 173.5(CO), 161.6 ('*ipso*'-Ph), 145.9 ('*m*'-Ph), 122.5 ('*o*'-Ph), 117.0 ('*p*'-Ph), 53.2 (OCH₃), 50.9 (CHala), 20.9 (CH₃ala).

**(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
O-[4-fluorophenyl-(methoxy-L-alaninyl)]-phosphate. Cf1737.**

C₂₄H₂₉N₇O₅P₁F₁, MW=545.57

[0124] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (5ml) and 4-fluorophenyl-(methoxy-L-alaninyl)-phosphorochloridate (1.89ml, 1.05mmol, of a 0.56M solution in THF), at room temperature for 24hrs. The solvent was removed under reduced pressure and the residue columned in 2.5-5% methanol in chloroform, and then in 3% methanol in chloroform, to give the pure product as a pale yellow foamy solid (62.0mg, 32.5%).

³¹P NMR: δ 4.24, 4.23, 4.20, 4.19.

¹H NMR: δ 7.52 (1H,d,H8), 7.21-7.14 (2H,m,'*o*'-Ph), 7.03-6.97 (2H,m,'*m*'-Ph), 6.16 (1H,bs,NHcPr), 6.10-6.07 (1H,q, H2'), 5.93-5.89 (1H,q,H3'), 5.44 (1H,d,H1'), 5.14 (2H,bs,NH₂), 4.23-3.98 (4H,m,H5',NHala+CHala), 3.72 (3H,d,OCH₂), 3.16 (1H,d,J=6.03Hz,H4'), 3.03 (1H,d,CHcPr), 2.86-2.74 (1H,m,1 of H6'), 1.76-1.66 (1H,m,1 of H6'), 1.42-1.35 (3H,dd, CH₃ala), 0.89-0.83 (2H,q,2H of CH₂cPr), 0.65-0.60 (2H,t,2H of CH₂cPr).

¹³C NMR: δ 174.4(CO), 161.5 (C2), 160.3+156.6 ('*p*'-Ph), 156.6 (C4), 151.3 (C6), 150.2 ('*ipso*'-Ph), 136.8 (C2'), 136.0 (C8), 131.6 (C3'), 121.9 ('*o*'-Ph), 115.1 (C5), 69.3 (C5'), 59.3 (C1'), 52.9 (OCH₃), 50.6 (CHala), 46.0 (C4'), 34.9 (C6'), 24.2 (CHcPr), 21.3 (CH₃ala), 7.8 (CH₂cPr).

HPLC: t_R 31.536 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

4-iodophenyl-phosphorodichloridate

C₈H₄O₂P₁Cl₂I₁, MW=336.07

[0125] This was synthesised by a method analogous to that of 4-chlorophenylphosphorodichloridate, except using: Phosphorus oxychloride (3.29g, 2ml, 21.5mmol), and 4-iodophenol (4.72g, 21.5mmol) in anhydrous diethylether (60ml), and anhydrous triethylamine (2.71g, 3ml, 21.5mmol) in anhydrous diethylether (20ml). The reaction was stirred at -80°C for 4hrs, and then at room temperature for 2hrs. After filtration, and removal of the solvent, the product was obtained as a clear liquid (6.2g, 85.8%).

³¹P NMR: δ 4.72 (s).

¹H NMR: δ 7.71 (2H,d,J=8.59Hz,'*o*'-Ph), 7.06-7.02 (2H,dd,3=8.80Hz,'*m*'-Ph),

¹³C NMR: δ 149.9(''*ipso*''-Ph), 139.8 ('*m*'-Ph), 122.9 ('*o*'-Ph), 91.9 ('*p*'-Ph).

4-iodophenyl-(methoxy-L-alaninyl)-phosphorochloridate

C₁₀H₁₂N₁O₄P₁Cl₁I₁, MW=403.55

[0126] This was synthesised according to **Standard Procedure 3**, using L-alanine methyl ester hydrochloride salt (1.0g, 7.16mmol), 4-iodophenyl-phosphorodichloridate (2.41g, 7.16mmol), triethylamine (2ml, 14.3mmol) in DCM (70ml). The usual workup yielded the crude product as a yellow oil (3.59g, >100%), which was stored in THF (14ml) to give a 0.51M solution.

³¹P NMR: δ 9.31, 9.08 (1:1).

¹H NMR: 7.74-7.69(2H,m,'*o*'-Ph), 7.32-7.05 (2H,m,'*m*'-Ph), 4.73 (1H,bs,NHala), 4.20 (1H,bs,CHala), 3.81 (3H,d, OCH₃), 1.56-1.53 (3H,dd,J=7.06Hz,CH₃ala).

¹³C NMR: δ 173.4(CO), 149.9 ('*ipso*'-Ph), 139.5 ('*m*'-Ph), 123.0 ('*o*'-Ph), 90.4 ('*p*'-Ph), 53.3 (OCH₃), 50.9 (CHala), 20.9 (CH₃ala).

EP 1 117 669 B1

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol
O-[4-iodophenyl-(methoxy-L-alaninyl)]-phosphate. Cf1738.

$C_{24}H_{29}N_7O_5P_1I_1$, MW=653.48

5

[0127] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (5ml) and 4-iodophenyl-(methoxy-L-alaninyl)-phosphorochloridate (2.05ml, 1.05mmol, of a 0.51M solution in THF), at room temperature for 48hrs. The solvent was removed under reduced pressure and the residue columned in 3-6% methanol in chloroform, and then in 3% methanol in chloroform, to give the pure product as a white foamy solid (82.0mg, 29.9%).

10

^{31}P NMR: δ 3.92 (s).

1H NMR: δ 7.63-7.59 (2H,dd,J=8.65Hz,'*m'*-Ph), 6.98 (2H,t,J=8.20Hz'*o'*-Ph), 6.25 (1H,bs,NHcPr), 6.09 (1H,t,H2'), 5.91 (1H,t,H3'), 5.54 (1H,d,H1'), 5.21 (2H,bs,NH₂), 4.35-4.16 (3H,m,H5',NHala), 4.07-3.95 (1H,m,CHala), 3.71 (3H,d, OCH₃ala), 3.15 (1H,d,J=7.23Hz,H4'), 3.03 (1H,bs,CHcPr), 2.85-2.74 (1H,m,1of H6'), 1.76-1.65 (1H,m,1of H6'), 1.43-1.35 (3H,t,CH₃ala), 0.89-0.83 (2H,q,2Hof CH₂cPr), 0.63 (2H,bs,2Hof CH₂cPr).

15

^{13}C NMR: δ 174.4(CO) 160.2 (C2), 156.5 (C4), 151.1 (C6) 151.0 ('*ipso'*-Ph), 139.0 (C2'), 136.8 ('*m'*-Ph), 136.0 (C8), 131.5 (C3'), 122.8 ('*o'*-Ph), 115.0 (C5), 88.9 ('*p'*-Ph), 69.4 (C5'), 59.3 (C1'), 52.9 (OCH₃), 50.6 (CHala), 46.0 (C4'), 34.8 (C6'), 24.2 (CHcPr), 21.3 (CH₃ala), 7.8 (CH₂cPr).

20

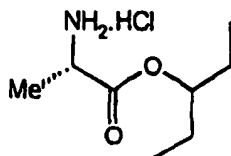
HPLC: t_R 33.848 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

L-Alanine (3-pentyl) ester hydrochloride salt

[0128]

25

30



35

[0129] Thionyl chloride (1.6 ml, 0.022 M) was added dropwise to a stirred solution of 3-pentanol (18.2 ml, 0.17 M) at 0 °C under nitrogen. The mixture was stirred for 30 minutes, then allowed to warm to room temperature. L-Alanine (pre-dried at 60 °C over P₂O₅ for 4 hrs: 1.0 g, 0.011 M) was added and the resulting suspension was heated at reflux overnight (the reaction mixture became a clear, colourless solution). The solvent was removed under reduced pressure to leave an oil which was repeatedly triturated and coevaporated with diethyl ether, then petrol (60/80) to remove traces of 3-pentanol. The resulting oily residue solidified on drying under high vacuum to give a peach-coloured solid (1.96 g, 10 mmol, 89 %).

40

δ_H (d_4 -CH₃OH, 300 MHz) 0.94 (t, 6H, O-CH(CH₂CH₃)₂, *J* = 7), 1.57 (d, 3H, CH₃-ala, *J* = 7), 1.67 (m, 4H, O-CH(CH₂CH₃)₂, *J* = 7), 4.12 (q, 1H, CH-ala, *J* = 7), 4.88 [m, 1H, O-CH(C₂H₅)₂]; δ_C (d_4 -CH₃OH, 75 MHz) 8.87 [O-CH(CH₂CH₃)₂], 15.38 (CH₃-ala), 26.39, 26.44 [O-CH(CH₂CH₃)₂], 48.82 (CH-ala), 79.88 [O-CH(C₂H₅)₂], 170.03 (C=O).

45

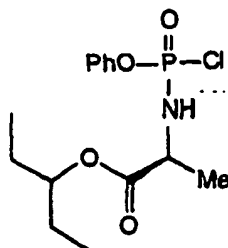
50

55

EP 1 117 669 B1

Phenyl(3-pentyloxy-L-alaninyl)phosphorochloridate

[0130]



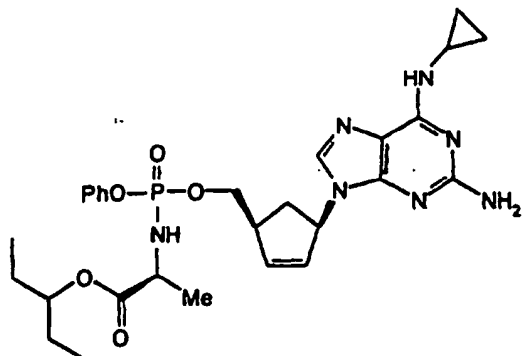
[0131] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.45 ml, 3.0 mmol), dry triethylamine (0.8 ml, 6.0 mmol), L-alanine (3-pentyl) ester hydrochloride salt 1a (0.583 g, 3.0 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, pale yellow oil (1.055 g, >100 %).

δ_P (CDCl₃, 121 MHz) 8.99, 9.37

[0132] The product was redissolved in dry THF (5 ml) and used as a 0.211 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(3-pentyloxy-L-alaninyl)phosphate] [Cf 1685]

[0133]

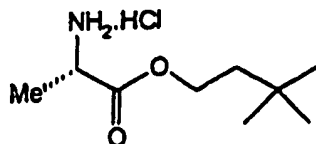


[0134] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^tBuMgCl (1.0 M in THE: 1.4 ml, 1.4 mmol), phenyl(3-pentyloxy-L-alaninyl) phosphor-ochloridate **1b** (3.3 ml of 0.211 g/ml solution, 2.1 mmol) and dry THE (8 ml). TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 1.5 hrs. The crude residue was purified twice by column chromatography, using (i) MeOH:CHCl₃ (4:96) and (ii) MeOH:CHCl₃ (3:97) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.202 g, 0.35 mmol, 50 %). δ_P (CDCl₃, 121 MHz) 3.89; δ_H (CDCl₃, 300 MHz) 0.66 (m, 2H, CH₂-cPr), 0.90 [m, 8H, CH₂-cPr and CH(CH₂CH₃)₂], 1.43 (m, 3H, CH₃-ala), 1.58 [m, 4H, CH(CH₂CH₃)₂], 1.72 (m, 1H, 6'H_a), 2.82 (m, 1H, 6'H_b), 3.05 (m, 1H, CH-cPr), 3.20 (m, 1H, 4'H), 3.77 (m, 1H, CH-ala), 4.05 (m, 1H, NH-ala), 4.22 (m, 2H, 5'H), 4.80 (m, 1H, O-CH-), 4.89 (bs, 2H, NH₂), 5.56 (m, 1H, 1'H), 5.78 (bs, 1H, NH-cPr), 5.93 (m, 1H, 3'H), 6.12 (m, 1H, 2'H), 7.26 (m, 5H, ArH), 7.51 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 6.37 (CH₂-cPr), 8.50 [CH(CH₂CH₃)₂], 20.28 (CH₃-ala), 22.68 (CH-cPr), 25.28, 25.38 [CH(CH₂CH₃)₂], 33.51, 33.60 (6'C), 44.59, 44.69 (4'C), 49.40 (CH-ala), 57.79, 57.83 (1'C), 67.90 (5'C), 77.29 (OCH), 113.86 (5C), 119.10-119.18 (o-Ph), 123.84 (p-Ph), 128.61 (m-Ph), 130.09, 130.16 (3'C), 134.45, 134.56 (8C), 135.27, 135.41 (2'C), 149.66-149.93 (6C and *ipso*-Ph), 155.26 (4C), 158.95 (2C), 172.32, 172.44 (C=O); *m/z* (FAB) 584.2751 (MH⁺, C₂₈H₃₉N₇O₅P requires 584.2750).

EP 1 117 669 B1

L-Alanine (3,3-dimethyl-1-butyl) ester hydrochloride salt

[0135]

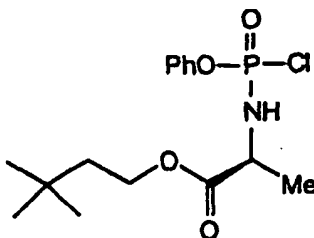


[0136] Prepared according to **Standard Procedure 2**, from L-alanine (1.6 g, 18 mmol), *p*-TSA monohydrate (3.8 g, 20 mmol), 3,3-dimethyl butan-1-ol (2.2 ml, 18 mmol) and toluene (100 ml). Conversion to the hydrochloride salt: the *p*-toluene sulfonate salt was redissolved in CHCl_3 and washed with 10 % potassium carbonate solution and water. The organic layer was dried (MgSO_4), filtered and the solvent was removed under reduced pressure to give the crude product as an oil. Aq. HCl (1 M), was added and the solution stirred for 30 minutes at room temperature. The solution was freeze-dried to give the hydrochloride salt as a white solid (3.31 g, 15.8 mmol, 88 %).

δ_{H} (d_4 - CH_3OH , 300 MHz) 0.93 [s, 9H, $\text{O}-(\text{CH}_2)_2(\text{CH}_3)_3$], 1.50 (d, 3H, CH_3 -ala, $J = 7$), 1.59 (t, 2H, $\text{O}-\text{CH}_2\text{CH}_2$, $J = 7$), 4.05 (q, 1H, CH-ala, $J = 7$), 4.25 (m, 2H, $\text{O}-\text{CH}_2$); δ_{C} (d_4 - CH_3OH , 75 MHz) 15.18 (CH_3 -ala), 28.91 [$\text{C}(\text{CH}_3)_3$], 29.54 [$\text{C}(\text{CH}_3)_3$], 41.62 ($\text{O}-\text{CH}_2\text{CH}_2$ -), 48.85 (CH-ala), 64.11 ($\text{O}-\text{CH}_2\text{CH}_2$ -), 170.03 ($\text{C}=\text{O}$).

Phenyl(3,3-dimethyl-1-butoxy-L-alanyl)phosphorochloridate

[0137]



[0138] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.45 ml, 3.0 mmol), dry triethylamine (0.8 ml, 6.0 mmol), L-alanine (3,3-dimethyl-1-butyl) ester hydro-chloride salt **2a** (0.632 g, 3.0 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, pale yellow oil (1.038 g, 99 %).

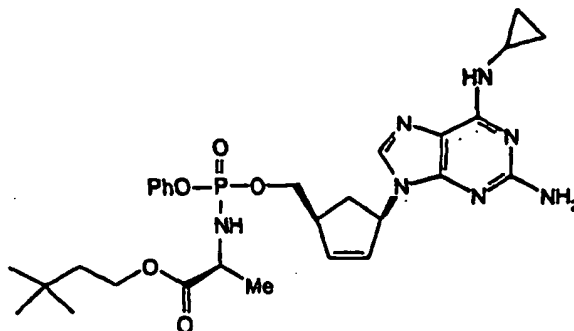
δ_{P} (CDCl_3 , 121 MHz) 8.94, 9.30

[0139] The product was redissolved in dry THE (5 ml) and used as a 0.208 g/ml solution.

EP 1 117 669 B1

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(3,3-dimethyl-1-butoxy-L-alaninyl)phosphate] [Cf 1687]

[0140]

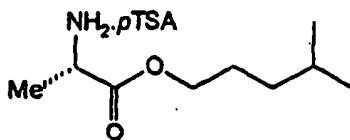


[0141] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^tBuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol), phenyl (3,3-dimethyl-1-butoxy-L-alaninyl) phosphorochloridate **2b** (3.5 ml of 0.208 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 1.5 hrs. The crude residue was purified twice by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.287 g, 0.5 mmol, 69 %).

δ_P (CDCl₃, 121 MHz) 3.83; δ_H (CDCl₃, 300 MHz) 0.66 (m, 2H, CH₂-cPr), 0.90 (m, 2H, CH₂-cPr), 0.97 [s, 9H, C(CH₃)₃], 1.41 (m, 3H, CH₃-ala), 1.57 (m, 2H, O-CH₂CH₂), 1.74 (m, 1H, 6'H_a), 2.82 (m, 1H, 6'H_b), 3.05 (m, 1H, CH-cPr), 3.20 (m, 1H, 4'H), 3.70 (m, 1H, CH-ala), 4.04 (m, 1H, NH-ala), 4.22 (m, 4H, 5'H and O-CH₂CH₂), 4.88 (bs, 2H, NH₂), 5.57 (m, 1H, 1'H), 5.75 (bs, 1H, NH-cPr), 5.93 (m, 1H, 3'H), 6.12 (m, 1H, 2'H), 7.27 (m, 5H, ArH), 7.52 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 6.35 (CH₂-cPr), 19.95, 20.01 (CH₃-ala), 22.69 (CH-cPr), 28.52 [C(CH₃)₃], 28.52 [C(CH₃)₃], 33.49, 33.57 (6'C), 40.59, 40.63 (OCH₂CH₂-), 44.58, 44.68 (4'C), 49.28 (CH-ala), 57.79, 57.83 (1'C), 62.28, 62.31 (OCH₂CH₂-), 67.86, 67.94 (5'C), 113.81 (SC), 119.10, 119.16 (*p*-Ph), 123.84 (*o*-Ph), 128.61 (*m*-Ph), 130.10, 130.16 (3'C), 134.47, 134.56 (8C), 135.29, 135.40 (2'C), 149.67-149.75 (6C and *ipso*-Ph), 155.25 (4C), 158.96 (2C), 172.55, 172.65 (C=O); *m/z* (FAB) 598.2896 (MH⁺, C₂₉H₄₁N₇O₅P requires 598.2907).

L-Alanine (4-methyl-1-pentyl) ester *p*-toluene sulfonate salt

[0142]

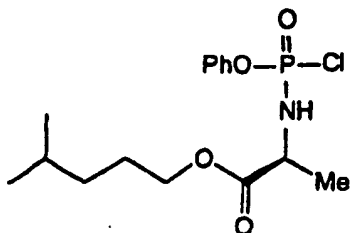


[0143] Prepared according to **Standard Procedure 2**, from L-alanine (1.6 g, 18 mmol), *p*-TSA monohydrate (3.8 g, 20 mmol), 4-methyl pentan-1-ol (2.24 ml, 18 mmol) and toluene (100 ml). The *p*-toluene sulfonate salt was isolated as a white solid (6.082 g, 17.6 mmol, 98 %). δ_H (d₄-CH₃OH, 300 MHz) 0.93 [d, 6H, CH(CH₃)₂], 1.27 (m, 2H, O-CH₂CH₂CH₂-), 1.54 (d, 3H, CH₃-ala), 1.59 [m, 1H, CH(CH₃)₂], 1.69 [m, 2H, O-(CH₂)₂CH₂], 2.39 (s, 3H, CH₃, *p*-TSA), 4.10 (m, 1H, CH-ala), 4.24 (m, 2H, O-CH₂), 7.25 (d, 2H, ArH, *p*-TSA), 7.72 (d, 2H, ArH, *p*-TSA); δ_C (d₄-CH₃OH, 75 MHz) 15.23 (CH₃-ala), 20.31 (CH₃-*p*TSA), 21.83 [CH(CH₃)₂], 26.45 (O-CH₂CH₂CH₂-), 27.87 [CH(CH₃)₂], 34.93 (O-CH₂CH₂CH₂-), 48.85 (CH-ala), 66.77 [O-CH₂(CH₂)₂], 125.93 (*o*-Ph, *p*-TSA), 128.83 (*m*-Ph, *p*-TSA), 140.75 (*ipso*-C-CH₃, *p*-TSA), 142.39 (*ipso*-C-S, *p*-TSA), 170.07 (C=O).

EP 1 117 669 B1

Phenyl(4-methyl-1-pentyloxy-L-alaninyl)phosphorochloridate

[0144]



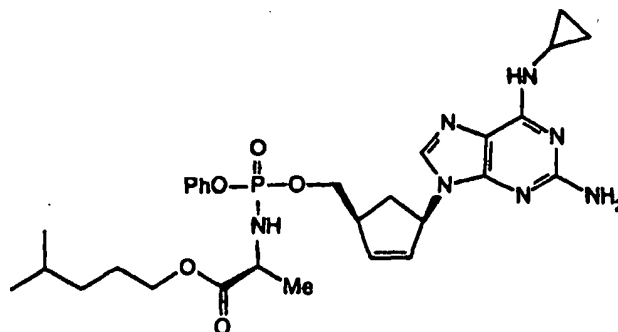
[0145] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.9 ml, 6.0 mmol), dry triethylamine (1.7 ml, 12.0 mmol), L-alanine (4-methyl-1-pentyl) ester *p*-toluene sulfonate salt **3a** (2.081 g, 6.0 mmol) and dry DCM (100 ml total). The crude product was obtained as a clear, colourless oil (1.79 g, 85 %).

δ_P (CDCl₃, 121 MHz) 8.95, 9.31

[0146] The product was redissolved in dry THF (10 ml) and used as a 0.179 g/ml solution.

(1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl (4-methyl-1-pentyloxy-L-alaninyl)phosphate] [Cf1721]

[0147]



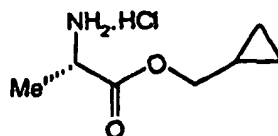
[0148] Prepared according to **Standard Procedure 4**, from (1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^tBuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol), phenyl(4-methyl-1-pentyloxy-L-alaninyl)phosphorochloridate **3b** (4.1 ml of 0.179 g/ml solution, 2.1 mmol) and dry THF (10 ml). TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 3 hrs. The crude residue was purified by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.288 g, 0.5 mmol, 69 %).

δ_P (CDCl₃, 121 MHz) 3.84, 3.88; δ_H (CDCl₃, 300 MHz) 0.64 (m, 2H, CH₂-cPr), 0.87 (m, 2H, CH₂-cPr), 1.24 [m, 2H, CH(CH₃)₂], 1.40 (t, 3H, CH₃-ala), 1.60 [m, 3H, CH(CH₃)CH₃], 1.73 [m, 3H, CH(CH₃)CH₃], 2.19 (m, 1H, 6'^H_a), 2.80 (m, 1H, 6'^H_b), 3.03 (m, 1H, CH-cPr), 3.18 (m, 1H, 4'^H), 3.88 (m, 1H, CH-ala), 4.03 (m, 3H, OCH₂- and NH-ala), 4.21 (m, 2H, 5'^H), 4.99 (bs, 2H, NH₂), 5.55 (m, 1H, 1'^H), 5.91 (m, 2H, NH-cPr and 3'^H), 6.10 (m, 1H, 2'^H), 7.29 (m, 5H, ArH), 7.51 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 7.79 (CH₂-cPr), 21.55 (CH₃-ala), 21.61 [CH(CH₃)₂], 23.69 (CH-cPr), 25.66 (O-CH₂CH₂CH₂-), 29.63 [CH(CH₃)₂], 35.00 (6'^C), 38.81 (O-CH₂CH₂CH₂-), 46.01, 46.11 (4'^C), 50.72 (CH-ala), 59.21 (1'^C), 69.31 (5'^C), 69.85 (O-CH₂CH₂-), 115.25 (5C), 120.52-120.62 (*p*-Ph), 125.25 (*o*-Ph), 130.04 (*m*-Ph), 131.59 (3'^C), 135.98 (8C), 136.71, 136.79 (2'^C), 151.08, 151.17 (6C and *ipso*-Ph), 156.70 (4C), 160.40 (2C), 174.00, 174.10 (C=O); *m/z* (FAB) 598.2883 (MH⁺, C₂₉H₄₁N₇O₅P requires 598.2907).

EP 1 117 669 B1

L-Alanine (cyclopropyl methyl) ester hydrochloride salt

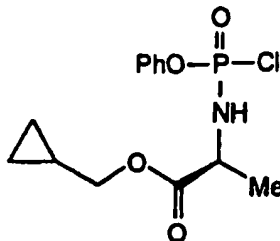
[0149]



[0150] Thionyl chloride (1.2 ml, 0.017 M) was added dropwise to a stirred solution of cyclopropyl methanol (6.8 ml, 8.4 mmol) at 0 °C under nitrogen. The mixture was stirred for 30 minutes, then allowed to warm to room temperature. L-Alanine (pre-dried at 60 °C over P₂O₅ for 4 hrs: 0.75 g, 8.4 mmol) was added and the resulting suspension was heated at reflux overnight (the reaction mixture became a clear, colourless solution). The solvent was removed under reduced pressure to leave an orange/red oil which was repeatedly triturated and coevaporated with diethyl ether, to remove traces of cyclopropyl methanol. Diethyl ether (~200 ml) was added and the mixture was stirred for 30 min. The resulting suspension was filtered to give the product as a cream solid (1.29 g, 7.1 mmol, 85 %). δ_H (*d*₄-CH₃OH, 300 MHz) 0.38 (m, 2H, CH₂-cPr), 0.65 (m, 2H, CH₂-cPr), 1.24 (m, 1H, CH-cPr), 1.60 (d, 3H, CH₃-ala, *J* = 7), 4.13 (m, 3H, CH-ala and O-CH₂); δ_C (*d*₄-CH₃OH, 75 MHz) 4.17 (CH₂-cPr), 10.98 (CH-cPr), 16.72 (CH₃-ala), 50.33 (CH-ala), 72.70 (O-CH₂), 171.56 (C=O).

Phenyl(cyclopropyl methoxy-L-alaninyl)phosphorochloridate

[0151]



[0152] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.9 ml, 6.0 mmol), dry triethylamine (1.7 ml, 12.0 mmol), L-alanine (cyclopropyl methyl) ester *p*-toluene sulfonate salt **4a** (1.082 g, 6.0 mmol) and dry DCM (100 ml total). The crude product was obtained as a clear, yellow oil (1.79 g, 94 %).

δ_P (CDCl₃, 121 MHz) 9.00, 9.36

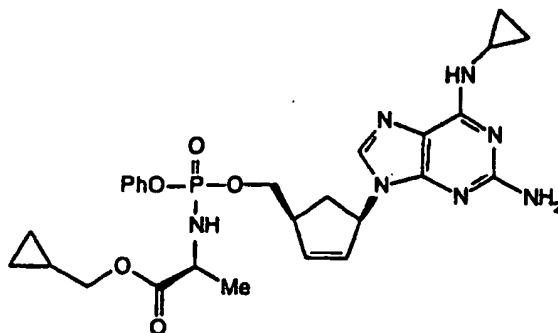
[0153] The product was redissolved in dry THF (5 ml) and used as a 0.385 g/ml solution.

EP 1 117 669 B1

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(cyclopropyl methoxy-L-alaninyl)]phosphate

[Cf 1774]

[0154]

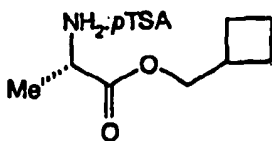


[0155] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^tBuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(cyclopropyl methoxy-L-alaninyl) phosphorochloridate **4b** (1.85 ml of 0.385 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 3.5 hrs. The crude residue was purified twice by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.244 g, 0.4 mmol, 61 %).

δ_P (CDCl₃, 121 MHz) 3.88, 3.94; δ_H (CDCl₃, 300 MHz) 0.29 (m, 2H, CH₂-cPr), 0.61 (m, 2H, CH₂-cPr), 0.87 (m, 2H, CH₂-cPr), 1.17 (m, 1H, CH-cPr), 1.42 (t, 3H, CH₃-ala), 1.69 (m, 1H, 6'H_a), 2.81 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.18 (m, 1H, 4'H), 4.01 (m, 4H, OCH₂-, CH-ala and NH-ala), 4.21 (m, 2H, 5'H), 5.03 (bs, 2H, NH₂), 5.56 (m, 1H, 1'H), 5.91 (m, 1H, 3'H), 6.05 (bs, 1H, NH-cPr), 6.10 (m, 1H, 2'H), 7.25 (m, 5H, ArH), 7.51 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 2.24 (CH₂-cPr), 6.33 (CH₂-cPr), 8.66 (CH₂-cPr), 20.05, 20.11 (CH₃-ala), 22.68 (CH-cPr), 33.55 (6'C), 44.58, 44.68 (4'C), 49.24, 49.31 (CH-ala), 57.77, 57.82 (1'C), 67.76, 67.93 (O-CH₂), 69.27, 69.29 (5'C), 113.74 (5C), 119.10-119.19 (*p*-Ph), 123.84 (*o*-Ph), 128.61 (*m*-Ph), 130.09, 130.13 (3'C), 134.42, 134.50 (8C), 135.32, 135.40 (2'C), 149.66, 149.74 (6C and *ipso*-Ph), 155.26 (4C), 159.00 (2C), 172.64, 172.73 (C=O).

L-Alanine (cyclobutyl methyl) ester hydrochloride salt

[0156]

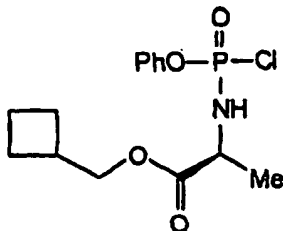


[0157] Prepared according to **Standard Procedure 2**, from L-alanine (1.6 g, 18 mmol), *p*-TSA monohydrate (3.8 g, 20 mmol), cyclobutane methanol (1.9 ml, 20 mmol) and toluene (100 ml). The *p*-toluene sulfonate salt was isolated as a white solid (4.249 g, 12.9 mmol, 72 %). δ_H (d₄-CH₃OH, 300 MHz) 1.54 (d, 3H, CH₃-ala, *J* = 7), 1.89 (m, 4H, cBu-2/4H), 2.08 (m, 2H, cBu-3H), 2.39 (s, 3H, CH₃, *p*-TSA), 2.69 (m, 1H, CH-cBu), 4.11 (q, 1H, CH-ala, *J* = 7), 4.22 (m, 2H, O-CH₂), 7.26 (d, 2H, ArH, *p*-TSA), 7.73 (d, 2H, ArH, *p*-TSA); δ_C (d₄-CH₃OH, 75 MHz) 16.7 (CH₃-ala), 19.6 (CH₂-cBu), 21.7 (CH₃-*p*TSA), 25.9 (CH₂-cBu), 35.7 (CH-cBu), 48.9 (CH-ala), 71.3 (O-CH₂), 127.4 (*o*-Ph, *p*-TSA), 130.3 (*m*-Ph, *p*-TSA), 142.2 (*ipso*-C-CH₃, *p*-TSA), 143.8 (*ipso*-C-S, *p*-TSA), 171.6 (C=O).

EP 1 117 669 B1

Phenyl(cyclobutyl methoxy-L-alaninyl)phosphorochloridate

[0158]



[0159] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.9 ml, 6.0 mmol), dry triethylamine (1.7 ml, 12.0 mmol), L-alanine (cyclobutyl methyl) ester *p*-toluene sulfonate salt **5a** (1.98 g, 6.0 mmol) and dry DCM (100 ml total). The crude product was obtained as a clear, colourless oil (2.04 g, >100 %).

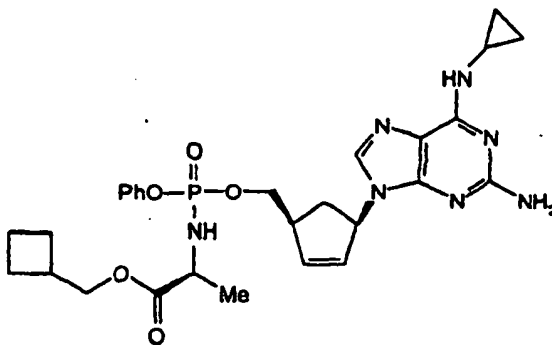
δ_P (CDCl₃, 121 MHz) 9.00, 9.34

[0160] The product was redissolved in dry THF (5 ml) and used as a 0.408 g/ml solution.

(1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(cyclobutyl methoxy-L-alaninyl)]phosphate

[Cf 1773]

[0161]



[0162] Prepared according to **Standard Procedure 4**, from (1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^tBuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(cyclobutyl methoxy-L-alaninyl) phosphorochloridate **5b** (1.7 ml of 0.408 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 3 hrs. The crude residue was purified twice by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.213 g, 0.4 mmol, 52 %).

δ_P (CDCl₃, 121 MHz) 3.87, 3.91; δ_H (CDCl₃, 300 MHz) 0.65 (m, 2H, CH₂-cPr), 0.89 (m, 2H, CH₂-cPr), 1.41 (t, 3H, CH₃-ala), 1.74 (m, 3H, CH₂-cBu and 6'H_a), 2.06 (m, 2H, CH₂-cBu), 2.61 (m, 2H, CH₂-cBu), 2.81 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.19 (m, 1H, 4'H), 3.90 (m, 1H, NH-ala), 4.09 (m, 3H, OCH₂- and CH-ala), 4.22 (m, 2H, 5'H), 4.98 (bs, 2H, NH₂), 5.56 (m, 1H, 1'H), 5.92 (m, 2H, 3'H and NH-cPr), 6.11 (m, 1H, 2'H), 7.26 (m, 5H, ArH), 7.52 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 6.37 (CH₂-cPr), 17.33 (CH₂-cBu), 20.17, 20.23 (CH₃-ala), 22.68 (CH-cPr), 23.57 (2 × CH₂-cBu), 32.86 (CH-cBu), 33.51, 33.55 (6'C), 44.58, 44.68 (4'C), 49.23, 49.28 (CH-ala), 57.81, 57.85 (1'C), 67.78-67.94 (5'C), 68.17, 68.20 (O-CH₂), 113.83 (SC), 119.09-119.19 (*p*-Ph), 123.87 (*o*-Ph), 128.62 (*m*-Ph), 130.11, 130.15 (3'C), 134.51,

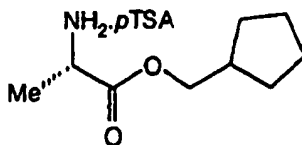
EP 1 117 669 B1

134.61 (8C), 135.30, 135.39 (2'C), 149.64-149.97 (6C and *ipso*-Ph), 155.20 (4C), 158.87 (2C), 172.64, 172.74 (C=O).

L-Alanine (cyclopentyl methyl) ester *p*-toluene sulfonate salt

5 [0163]

10



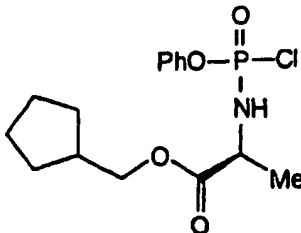
15

[0164] Prepared according to **Standard Procedure 2**, from L-alanine (1.6 g, 18 mmol), *p*-TSA monohydrate (3.8 g, 20 mmol), cyclopentane methanol (1.9 ml, 18 mmol) and toluene (100 ml). The *p*-toluene sulfonate salt was isolated as a white solid (6.21 g, 18 mmol, 100 %). δ_H (d_4 -CH₃OH, 300 MHz) 1.22 (m, 2H, cPent 2/5H_a), 1.46 (d, 3H, CH₃-ala), 1.56 (m, 4H, cPent 2/3/4/5H_b), 1.70 (m, 2H, cPent 3/4H_a), 2.19 (m, 1H, CH-cPent), 2.31 (s, 3H, CH₃, *p*-TSA), 4.06 (m, 3H, O-CH₂ and CH-ala), 7.18 (d, 2H, ArH, *p*-TSA), 7.64 (d, 2H, ArH, *p*-TSA); δ_C (d_4 -CH₃OH, 75 MHz) 15.25 (CH₃-ala), 20.30 (CH₃, *p*-TSA), 25.27 (CH₂-cPent), 29.10, 29.15 (CH₂-cPent), 38.72 (CH-cPent), 48.84 (CH-ala), 70.12 (O-CH₂), 125.93 (*o*-Ph, *p*-TSA), 128.82 (*m*-Ph, *p*-TSA), 140.75 (*ipso*-C-CH₃, *p*-TSA), 142.40 (*ipso*-C-S, *p*-TSA), 170.09 (C=O).

25 **Phenyl(cyclopentyl methoxy-L-alaninyl)phosphorochloridate**

[0165]

30



40

[0166] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.9 ml, 6.0 mmol), dry triethylamine (1.7 ml, 12.0 mmol), L-alanine (cyclopentane methyl) ester *p*-toluene sulfonate salt 6a (2.069 g, 6.0 mmol) and dry DCM (100 ml total). The crude product was obtained as a clear, yellow oil (1.97 g, 95 %).

45 δ_P (CDCl₃, 121 MHz) 8.94, 9.30

[0167] The product was redissolved in dry THF (10 ml) and used as a 0.197 g/ml solution.

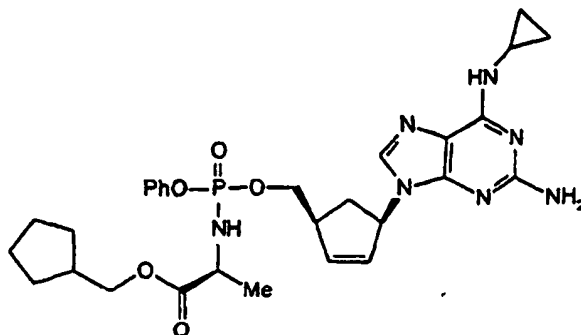
50

55

EP 1 117 669 B1

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(cyclopentyl methoxy-L-alaninyl)phosphate] [Cf 1722]

[0168]

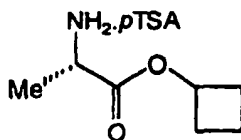


[0169] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^tBuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol), phenyl (cyclopentane methoxy-L-alaninyl) phosphorochloridate **6b** (3.7 ml of 0.197 g/ml solution, 2.1 mmol) and dry THF (10 ml). TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 3 hrs. The crude residue was purified by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.314 g, 0.5 mmol, 75 %).

δ_P (CDCl₃, 121 MHz) 3.86, 3.87; δ_H (CDCl₃, 300 MHz) 0.65 (m, 2H, CH₂-cPr), 0.89 [m, 8H, CH₂-cPr and (CH₂)₃-cPent], 1.24 (m, 2H, CH₂-cPent), 1.41 (m, 3H, CH₃-ala), 1.65 (m, 2H, CH-cPent and 6'H_a), 2.81 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.19 (m, 1H, 4'H), 3.80 (m, 1H, CH-ala), 4.07 (m, 3H, OCH₂ and NH-ala), 4.22 (m, 2H, 5'H), 4.92 (bs, 2H, NH₂), 5.55 (m, 1H, 1'H), 5.81 (bs, 1H, NH-cPr), 5.92 (m, 1H, 3'H), 6.11 (m, 1H, 2'H), 7.26 (m, 5H, ArH), 7.52 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 6.42 (CH₂-cPr), 21.43 (CH₃-ala), 22.73 (CH-cPr), 24.59 (CH₂-cPent), 25.35 (CH₂-cPent), 26.64 (CH-cPent), 33.43, 33.51 (6'C), 44.58, 44.68 (4'C), 49.23 (CH-ala), 57.86, 57.91 (1'C), 64.69, 64.97 (O-CH₂-), 67.84 (5'C), 113.74 (5C), 119.09-119.18 (*p*-Ph), 123.88 (*o*-Ph), 128.62 (*m*-Ph), 130.05, 130.11 (3'C), 134.65, 134.76 (8C), 135.33, 135.44 (2'C), 149.63, 149.72 (6C and *ipso*-Ph), 154.98 (4C), 158.59 (2C), 172.50, 172.60 (C=O); *m/z* (FAB) 598.2745 (MH⁺, C₂₉H₃₉N₇O₅P requires 596.2750).

L-Alanine (cyclobutyl) ester *p*-toluene sulfonate salt

[0170]



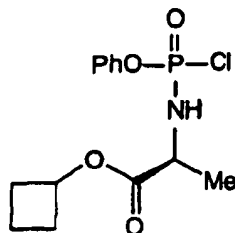
[0171] Prepared according to **Standard Procedure 2**, except using benzene as solvent: from L-alanine (1.0 g, 11 mmol), *p*-TSA monohydrate (2.35 g, 12 mmol), cyclobutanol (0.9 ml, 11 mmol) and benzene (65 ml). The *p*-toluene sulfonate salt was isolated as a white solid (1.73 g, 5.5 mmol, 49 %).

δ_H (d₄-CH₃OH, 300 MHz) 1.51 (d, 3H, CH₃-ala, *J* = 7), 1.75 (m, 2H, CH₂-cBu), 2.14 (m, 2H, CH₂-cBu), 2.37 (m, 5H, CH₂-cBu and CH₃, *p*-TSA), 4.05 (q, 1H, CH-ala, *J* = 7), 5.08 (m, 1H, CH-cBu), 7.24 (d, 2H, ArH, *p*-TSA), 7.70 (d, 2H, ArH, *p*-TSA); δ_C (d₄-CH₃OH, 75 MHz) 14.57 (CH₂-cBu), 16.58 (CH₃-ala), 21.73 (CH₃-*p*-TSA), 31.38, 31.44 (CH₂-cBu), 50.16 (CH-ala), 72.47 (CH-cBu), 127.35 (*o*-Ph, *p*-TSA), 130.23 (*m*-Ph, *p*-TSA), 142.13 (*ipso*-C-CH₃, *p*-TSA), 143.89 (*ipso*-C-S, *p*-TSA), 170.71 (C=O).

EP 1 117 669 B1

Phenyl(cyclobutoxy-L-alaninyl)phosphorochloridate

[0172]



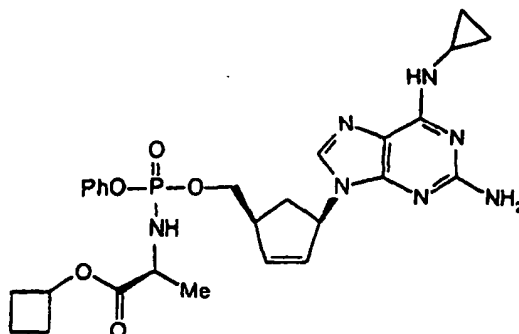
[0173] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.75 ml, 5.0 mmol), dry triethylamine (1.4 ml, 10.0 mmol), L-alanine (cyclopentane methyl) ester *p*-toluene sulfonate salt **7a** (1.58 g, 5.0 mmol) and dry DCM (65 ml total). The crude product was obtained as a clear, colourless oil (1.13 g, 71 %).

δ_P (CDCl₃, 121 MHz) 8.96, 9.33

[0174] The product was redissolved in dry THF (5 ml) and used as a 0.226 g/ml solution.

(1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(cyclobutoxy-L-alaninyl)]phosphate [Cf 1775]

[0175]



[0176] Prepared according to **Standard Procedure 4**, from (1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^tBuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(cyclobutyl methoxy-L-alaninyl) phosphorochloridate **7b** (2.95 ml of 0.226 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 3.5 hrs. The crude residue was purified by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a pale, yellow oil, which solidified to a cream solid after trituration and coevaporation with diethyl ether (0.238 g, 0.4 mmol, 60 %).

δ_P (CDCl₃, 121 MHz) 3.89, 3.93; δ_H (CDCl₃, 300 MHz) 0.63 (m, 2H, CH₂-cPr), 0.87 (m, 2H, CH₂-cPr), 1.39 (m, 3H, CH₃-ala), 1.65 (m, 2H, CH₂-cBu), 1.81 (m, 1H, 6'H_a), 2.04 (m, 2H, CH₂-cBu), 2.36 (m, 2H, CH₂-cBu), 2.80 (m, 1H, 6'H_b), 3.03 (m, 1H, CH-cPr), 3.17 (m, 1H, 4'H), 3.97 (m, 2H, NH-ala and CH-ala), 4.18 (m, 2H, 5'H), 4.98 (m, 3H, MH₂ and OCH), 5.55 (m, 1H, 1'H), 5.91 (m, 1H, 3'H), 6.01 (m, 1H, NH-cPr), 6.10 (m, 1H, 2'H), 7.25 (m, 5H, ArH), 7.51 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 7.80 (CH₂-cPr), 13.82 (CH₂-cBu), 21.42 (CH₃-ala), 22.06 (CH-cPr), 30.52-30.63 (CH₂-cBu), 35.01 (6'C), 46.01, 46.12 (4'C), 50.50 (CH-ala), 59.26 (1'C), 69.30 (CH-cBu), 70.19 (5'C), 115.25 (5C), 120.53, 120.59 (*p*-Ph), 125.28 (*o*-Ph), 130.05 (*m*-Ph), 131.53 (3'C), 135.97 (8C), 136.73, 136.85 (2'C), 151.08-151.17 (6C and

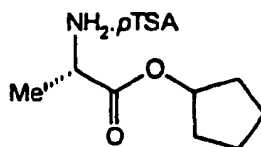
EP 1 117 669 B1

ipso-Ph), 156.71 (4C), 160.44 (2C), 173.33 (C=O).

L-Alanine (cyclopentyl) ester *p*-toluene sulfonate salt

5 [0177]

10



15

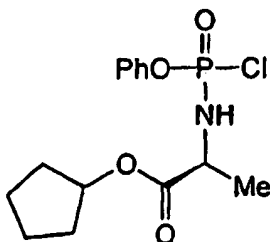
[0178] Prepared according to **Standard Procedure 2**, except using benzene as solvent: from L-alanine (1.6 g, 18 mmol), *p*-TSA monohydrate (3.8 g, 20 mmol), cyclopentanol (1.6 ml, 18 mmol) and benzene (100 ml). The *p*-toluene sulfonate salt was isolated as a beige solid (2.81 g, 8.5 mmol, 47 %).

20 δ_H (d_4 -CH₃OH, 300 MHz) 1.51 (d, 3H, CH₃-ala, $J = 7$), 1.71 (m, 6H, CH₂-cPnt), 1.92 (m, 2H, CH₂-cPnt), 2.39 (m, 5H, CH₂-cBu and CH₃, *p*-TSA), 4.04 (q, 1H, CH-ala, $J = 7$), 5.28 (m, 1H, CH-cPnt), 7.26 (d, 2H, ArH, *p*-TSA), 7.73 (d, 2H, ArH, *p*-TSA); δ_C (d_4 -CH₃OH, 75 MHz) 16.59 (CH₃-ala), 21.72 (CH₃-*p*TSA), 24.97 (CH₂-cPnt), 33.81, 33.97 (CH₂-cPnt), 50.31 (CH-ala), 81.37 (CH-cPnt), 127.36 (*o*-Ph, *p*-TSA), 130.25 (*m*-Ph, *p*-TSA), 142.20 (*ipso*-C-CH₃, *p*-TSA), 143.79 (*ipso*-C-S, *p*-TSA), 171.17 (C=O).

25 **Phenyl(cyclopentyloxy-L-alaninyl)phosphorochloridate**

[0179]

30



35

40

[0180] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.9 ml, 6.0 mmol), dry triethylamine (1.7 ml, 12.0 mmol), L-alanine (cyclopentane methyl) ester *p*-toluene sulfonate salt **8a** (1.98 g, 6.0 mmol) and dry DCM (100 ml total). The crude product was obtained as a clear, colourless oil (1.8 g, 91 %).

δ_P (CDCl₃, 121 MHz) 9.01, 9.37

45 [0181] The product was redissolved in dry THF (5 ml) and used as a 0.361 g/ml solution.

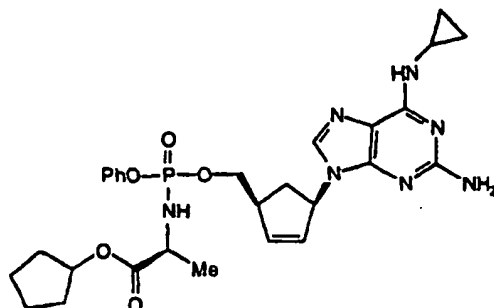
50

55

EP 1 117 669 B1

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(cyclopentoxyl-L-alaninyl)]phosphate [Cf 1776]

[0182]

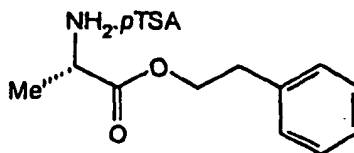


[0183] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^tBuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(cyclobutyl methoxy-L-alaninyl) phosphorochloridate **8b** (1.93 ml of 0.361 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 3.5 hrs. The crude residue was purified twice by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.254 g, 0.4 mmol, 62 %).

δ_P (CDCl₃, 121 MHz) 3.97, 3.98; δ_H (CDCl₃, 300 MHz) 0.64 (m, 2H, CH₂-cPr), 0.87 (m, 2H, CH₂-cPr), 1.38 (m, 3H, CH₃-ala), 1.67 (m, 7H, 3 × CH₂-cPent and 6'H₉), 1.86 (m, 2H, CH₂-cPent), 2.81 (m, 1H, 6'H₉), 3.04 (m, 1H, CH-cPr), 3.18 (m, 1H, 4'H), 3.96 (m, 2H, NH-ala and CH-ala), 4.21 (m, 2H, 5'H), 5.02 (bs, 1H, NH₂), 5.18 (m, 1H, OCH), 5.56 (m, 1H, 1'H), 5.91 (m, 1H, 3'H), 5.98 (bs, 1H, NH-cPr), 6.11 (m, 1H, 2'H), 7.25 (m, 5H, ArH), 7.51 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 7.78 (CH₂-cPr), 21.42, 21.48 (CH₃-ala), 24.07 (CH-cPr), 32.91- (CH₂-cPent), 33.05, 33.08 (6'C), 34.97, 35.02 (CH₂-cPent), 46.02, 46.12 (4'C), 50.71 (CH-ala), 59.21, 59.25 (1'C), 69.22, 69.29 (5'C), 78.90 (OCH), 115.23 (5C), 120.55- 120.61 (*p*-Ph), 125.28 (*o*-Ph), 130.05 (*m*-Ph), 131.53, 131.59 (3'C), 135.87, 135.97 (8C), 136.73, 136.86 (2'C), 151.09, 151.18 (6C and *ipso*-Ph), 156.71 (4C), 160.44 (2C), 173.71, 173.80(C=O).

L-Alanine (phenethyl) ester *p*-toluene sulfonate salt

[0184]

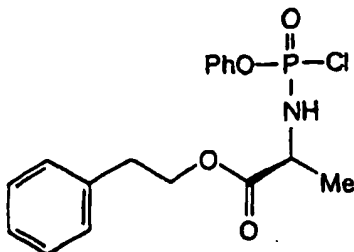


[0185] Prepared according to **Standard Procedure 2**, from L-alanine (1.0 g, 11 mmol), *p*-TSA monohydrate (2.35 g, 12 mmol), phenethyl alcohol (1.3 ml, 11 mmol) and toluene (65 ml). The *p*-toluene sulfonate salt was isolated as an off-white solid (4.0 g, 10.9 mmol, 97 %). δ_H (*d*₄-CH₃OH, 300 MHz) 1.46 (d, 3H, CH₃-ala, *J* = 7), 2.32 (2, 3H, CH₃, *p*-TSA), 2.93 (t, 2H, CH₂Ph, *J* = 7), 4.07 (q, 1H, CH-ala, *J* = 7), 4.37 (m, 2H, O-CH₂) 7.22 (m, 7H, ArH, *p*-TSA and PhH), 7.78 (d, 2H, ArH, *p*-TSA); δ_C (*d*₄-CH₃OH, 75 MHz) 16.80 (CH₃-ala), 22.06 (CH₃-*p*TSA), 36.20 (CH₂-Ph), 50.41 (CH-ala), 68.28 (O-CH₂), 127.70, 127.83 (*o*-Ar and *o*-Ph, *p*-TSA), 129.81 (*p*-Ar), 130.13, 130.48 (*m*-Ar and *m*-Ph, *p*-TSA), 139.23 (*ipso*-ArC), 142.30 (*ipso*-C-CH₃, *p*-TSA), 143.83 (*ipso*-C-S, *p*-TSA), 171.44 (C=O).

EP 1 117 669 B1

Phenyl(phenethoxy-L-alaninyl)phosphorochloridate

[0186]



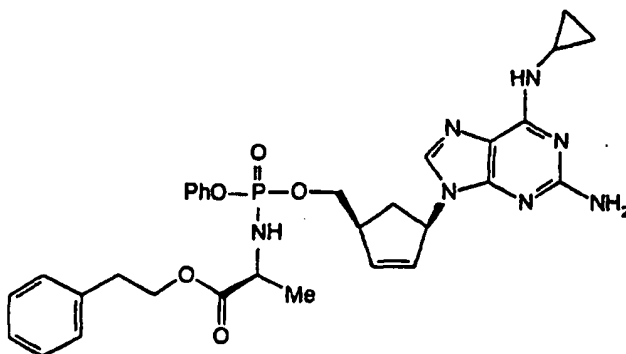
[0187] Prepared according to Standard Procedure 3, from phenyl dichlorophosphate (0.5 ml, 33 mmol), dry triethylamine (0.93 ml, 6.7 mmol), L-alanine (phenethyl) ester *p*-toluene sulfonate salt **9a** (1.232g, 3.3 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, colourless oil (1.16 g, 94 %).

δ_P (CDCl₃, 121 MHz) 8.93, 9.25

[0188] The product was redissolved in dry THF (5 ml) and used as a 0.233 g/ml solution.

(1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(phenethoxy-L-alaninyl)]phosphate [Cf 1777]

[0189]



[0190] Prepared according to Standard Procedure 4, from (1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^tBuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(phenethoxy-L-alaninyl) phosphor-ochloridate **9b** (3.3 ml of 0.233 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 3 hrs. The crude residue was purified twice by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a pale, yellow oil, which solidified to a cream solid after trituration and coevaporation with diethyl ether (0.181 g, 0.3 mmol, 42 %).

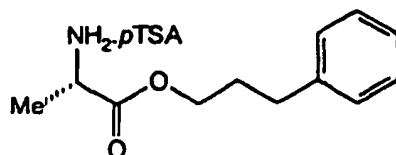
δ_P (CDCl₃, 121 MHz) 3.81, 3.86; δ_H (CDCl₃, 300 MHz) 0.65 (m, 2H, CH₂-cPr), 0.89 (m, 2H, CH₂-cPr), 1.35 (m, 3H, CH₃-ala), 1.71 (m, 1H, 6'H_a), 2.80 (m, 1H, 6'H_b), 2.96 (m, 2H, CH₂Ph), 3.03 (m, 1H, CH-cPr), 3.17 (m, 1H, 4'H), 3.91 (m, 2H, NH-ala and CH-ala), 4.18 (m, 2H, OCH), 4.36 (m, 2H, 5'H), 4.99 (bs, 1H, NH₂), 5.56 (m, 1H, 1'H), 5.92 (m, 2H, 3'H and NH-cPr), 6.09 (m, 1H, 2'H), 7.26 (m, 10H, ArH and PhH), 7.52 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 6.36 (CH₂-cPr), 19.98, 20.04 (CH₃-ala), 22.65 (CH-cPr), 33.46, 33.54 (6'C), 33.90 (CH₂-Ph), 44.56, 44.66 (4'C), 49.21 (CH-ala), 57.79, 57.85 (1'C), 64.84 (OCH₂), 67.82 (5'C), 113.79 (5C), 119.11-119.17 (*p*-Ph), 123.87 (*p*-Ar), 125.68 (*o*-Ph), 127.53 (*o*-Ar), 127.83 (*m*-Ph), 128.62 (*m*-Ar), 130.07, 130.14 (3'C), 134.48 (8C), 135.30, 135.39 (2'C), 136.25 (*ipso*-Ar),

EP 1 117 669 B1

149.63, 149.71 (6C and *ipso*-Ph), 155.25 (4C), 158.94 (2C), 172.75, 172.45 (C=O).

L-Alanine (3-phenyl-1-propyl) ester *p*-toluene sulfonate salt

[0191]



[0192] Prepared according to **Standard Procedure 2**, from L-alanine (1.0 g, 11 mmol), *p*-TSA monohydrate (2.35 g, 12 mmol), 3-phenyl-1-propanol (1.5 ml, 11 mmol) and toluene (65 ml). Removal of the solvent gave the crude product as a yellow oil. Diethyl ether was added and the mixture was cooled for 30 mins. The resulting suspension was filtered to give the *p*-toluene sulfonate salt as a white solid (4.24 g, 11.2 mmol, 100 %).

δ_H (d_4 -CH₃OH, 300 MHz) 1.53 (d, 3H, CH₃-ala, J = 7), 1.97 (m, 2H, CH₂CH₂Ph), 2.34 (2, 3H, CH₃, *p*-TSA), 2.67 (t, 2H, CH₂Ph, J = 7), 4.10 (q, 1H, CH-ala, J = 7), 4.20 (t, 2H, O-CH₂, J = 7) 7.22 (m, 7H, ArH, *p*-TSA and PhH), 7.75 (d, 2H, ArH, *p*-TSA); δ_C (d_4 -CH₃OH, 75 MHz) 16.77 (CH₃-ala), 21.93 (CH₃-*p*TSA), 31.63 (CH₂CH₂-Ph), 33.37 (CH₂-Ph), 50.44 (CH-ala), 67.27 (O-CH₂), 127.26-127.58 (*o*-Ar and *o*-Ph, *p*-TSA), 129.66-130.00 (*p*-Ar), 130.41 (*m*-Ar and *m*-Ph, *p*-TSA), 142.31 (*ipso*-ArC), 142.82 (*ipso*-C-CH₃, *p*-TSA), 143.82 (*ipso*-C-S, *p*-TSA), 171.47 (C=O).

Phenyl(phenethoxy-L-alaninyl)phosphorochloridate

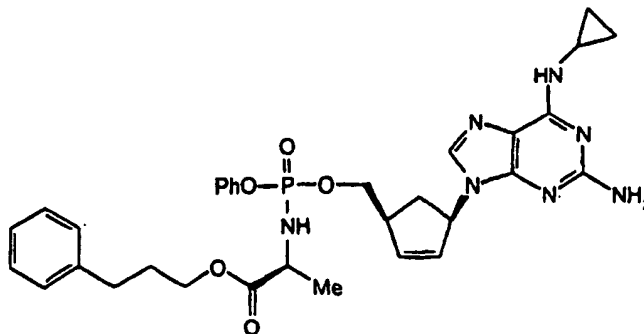
[0193] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.5 ml, 3.3 mmol), dry triethylamine (0.93 ml, 6.7 mmol), L-alanine (3-phenyl-1-propyl) ester *p*-toluene sulfonate salt **9a** (1.27g, 3.3 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, pale brown oil (1.16 g, 90 %).

δ_P (CDCl₃, 121 MHz) 8.94, 9.27

The product was redissolved in dry THF (5 ml) and used as a 0.231 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(3-phenyl-1-propoxy-L-alaninyl)]phosphate [Cf 1778]

[0194]



[0195] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^tBuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(3-phenyl-1-propoxy-L-alaninyl) phosphorochloridate **10b** (3.5 ml of 0.231 g/ml solution, 2.1 mmol) and dry THF (8 ml).

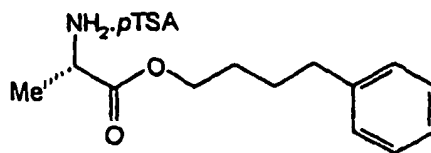
[0196] TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 4 hrs. The crude residue was purified

EP 1 117 669 B1

three times by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a pale, yellow oil, which solidified to an off-white foam after trituration and coevaporation with diethyl ether (0.330 g, 0.5 mmol, 75 %).
 δ_p (CDCl₃, 121 MHz) 3.89, 3.91; δ_H (CDCl₃, 300 MHz) 0.63 (m, 2H, CH₂-cPr), 0.88 (m, 2H, CH₂-cPr), 1.42 (m, 3H, CH₃-ala), 1.72 (m, 1H, 6'H_a), 1.98 (CH₂CH₂Ph), 2.69 (CH₂Ph), 2.80 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.18 (m, 1H, 4'H), 4.07 (m, 6H, NH-ala, CH-ala, OCH and 5'H), 5.00 (bs, 1H, NH₂), 5.56 (m, 1H, 1'H), 5.91 (m, 2H, 3'H and NH-cPr), 6.10 (m, 1H, 2'H), 7.25 (m, 10H, ArH and PhH), 7.52 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 6.35 (CH₂-cPr), 20.06, 20.12 (CH₃-ala), 22.65 (CH-cPr), 29.02 (CH₂CH₂Ph), 30.97 (CH₂Ph), 33.48, 33.55 (6'C), 44.57, 44.67 (4'C), 49.26 (CH-ala), 57.78, 57.84 (1'C), 63.84 (OCH₂), 67.88 (5'C), 113.83 (5C), 119.10, 119.15 (*p*-Ph and *p*-Ar), 123.86 (*o*-Ph), 125.09 (*o*-Ar), 127.33, 127.47 (*m*-Ph), 128.63 (*m*-Ar), 130.10, 130.17 (3'C), 134.47, 134.58 (8C), 135.27, 135.37 (2'C), 139.81 (*ipso*-Ar), 149.65, 149.74 (6C and *ipso*-Ph), 155.27 (4C), 158.98 (2C), 172.49, 172.58 (C=O).

L-Alanine (4-phenyl-1-butyl) ester *p*-toluene sulfonate salt

[0197]



25

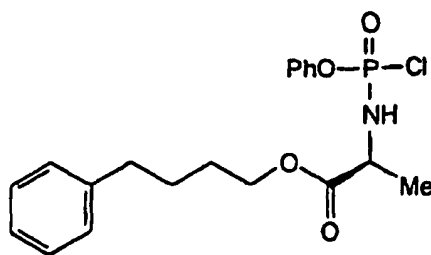
[0198] Prepared according to **Standard Procedure 2**, from L-alanine (1.0 g, 11 mmol), *p*-TSA monohydrate (2.35 g, 12 mmol), 4-phenyl-1-butanol (1.7 ml, 11 mmol) and toluene (65 ml). Removal of the solvent gave the crude product as a clear, colourless oil, which solidified to a white solid after trituration and coevaporation with petrol (60/80) (4.4 g, 11.2 mmol, 100 %).

δ_H (*d*₄-CH₃OH, 300 MHz) 1.55 (d, 3H, CH₃-ala, *J* = 7), 1.74 (m, 4H, -(CH₂)₂CH₂Ph), 2.41 (2, 3H, CH₃, *p*-TSA), 2.67 (m, 2H, CH₂Ph), 4.12 (q, 1H, CH-ala, *J* = 7), 4.28 (m, 2H, O-CH₂) 7.25 (m, 7H, ArH, *p*-TSA and PhH), 7.75 (d, 2H, ArH, *p*-TSA); δ_C (*d*₄-CH₃OH, 75 MHz) 16.65 (CH₃-ala), 21.74 (CH₃-*p*TSA), 29.18, 29.50 (OCH₂(CH₂)₂CH₂-Ph), 36.72 (CH₂-Ph), 50.27 (CH-ala), 67.74 (O-CH₂), 127.31, 127.36 (*o*-Ar and *o*-Ph, *p*-TSA), 129.79 (*p*-Ar), 130.25 (*m*-Ar and *m*-Ph, *p*-TSA), 142.14 (*ipso*-ArC), 143.64, 143.87 (*ipso*-C-CH₃ and *ipso*-C-S, *p*-TSA), 171.47 (C=O).

35

Phenyl(4-phenyl-1-butoxy-L-alaninyl)phosphorochloridate

[0199]



50

[0200] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.5 ml, 3.3 mmol), dry triethylamine (0.93 ml, 6.7 mmol), L-alanine (4-phenyl-1-butyl) ester *p*-toluene sulfonate salt **11a** (1.32g, 3.3 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, pale brown oil (1.13 g, 85 %).

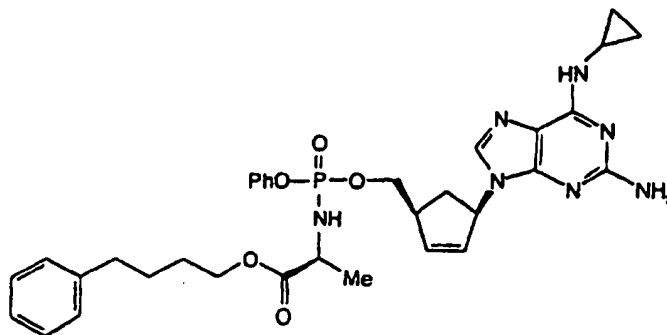
δ_p (CDCl₃, 121 MHz) 8.89, 9.24

[0201] The product was redissolved in dry THF (5 ml) and used as a 0.226 g/ml solution.

EP 1 117 669 B1

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl(4-phenyl-1-butoxy-L-alaninyl))phosphate [Cf 1779]

[0202]

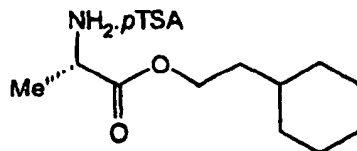


[0203] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^tBuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(4-phenyl-1-butoxy-L-alaninyl) phosphorochloridate **11b** (3.7 ml of 0.226 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 4 hrs. The crude residue was purified by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to an off-white foam after trituration and coevaporation with diethyl ether (0.314 g, 0.5 mmol, 69 %).

δ_p (CDCl₃, 121 MHz) 3.87, 3.90; δ_H (CDCl₃, 300 MHz) 0.65 (m, 2H, CH₂-cPr), 0.87 (m, 2H, CH₂-cPr), 1.41 (m, 3H, CH₃-ala), 1.71 (m, 5H, (CH₂)₂CH₂Ph and 6'H_a), 2.65 (m, 2H, CH₂Ph), 2.80 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.17 (m, 1H, 4'H), 4.06 (m, 6H, NH-ala, CH-ala, 5'H and OCH₂-), 5.02 (bs, 1H, NH₂), 5.56 (m, 1H, 1'H), 5.90 (m, 1H, 3'H), 5.98 (bs, 1H, NH-cPr), 6.10 (m, 1H, 2'H), 7.25 (m, 10H, ArH and PhH), 7.52 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 6.35 (CH₂-cPr), 20.05, 20.11 (CH₃-ala), 22.65 (CH-cPr), 26.51 (CH₂CH₂CH₂Ph), 27.02 (CH₂(CH₂)₂Ph), 33.48, 33.55 (6'C), 34.32 (CH₂Ph), 44.56, 44.67 (4'C), 49.22, 49.26 (CH-ala), 57.79, 57.83 (1'C), 64.40 (OCH₂), 67.86, 67.94 (5'C), 113.75 (5C), 119.10, 119.15 (*p*-Ph and *p*-Ar), 123.85 (*o*-Ph), 124.88 (*o*-Ar), 127.33, 127.35 (*m*-Ph), 128.61 (*m*-Ar), 130.07, 130.12 (3'C), 134.44, 134.54 (8C), 135.30, 135.39 (2'C), 140.76 (*ipso*-Ar), 149.64-149.87 (6C and *ipso*-Ph), 155.26 (4C), 158.98 (2C), 172.53, 172.63 (C=O).

L-Alanine (2-cyclohexyl ethyl) ester *p*-toluene sulfonate salt

[0204]



[0205] Prepared according to **Standard Procedure 2**, from L-alanine (1.0 g, 11 mmol), *p*-TSA monohydrate (2.35 g, 12 mmol), 2-cyclohexyl ethanol (1.56 ml, 11 mmol) and toluene (65 ml). Removal of the solvent gave the crude product as a clear, colourless oil, which solidified to a white solid after trituration and coevaporation with diethyl ether (2.8 g, 7.5 mmol, 67 %).

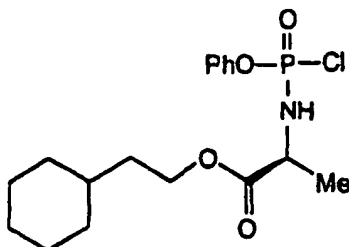
δ_H (*d*₄-CH₃OH, 300 MHz) 0.97 (m, 2H, CH₂), 1.24 (m, 4H, 2 × CH₂), 1.42 (m, 1H, CH-cHx), 1.54 (d, 3H, CH₃-ala, *J* = 7), 1.63 (m, 2H, CH₂), 1.75 (m, 4H, 2 × CH₂), 2.39 (s, 3H, CH₃, *p*-TSA), 4.09 (q, 1H, CH-ala, *J* = 7), 4.28 (m, 2H, O-CH₂), 7.25 (d, 2H, ArH, *p*-TSA), 7.72 (d, 2H, ArH, *p*-TSA); δ_C (*d*₄-CH₃OH, 75 MHz) 16.65 (CH₃-ala), 21.74 (CH₃-

EP 1 117 669 B1

ρ TSA), 27.68 (CH₂), 27.93 (CH₂), 34.58 (CH₂), 34.62 (CH₂), 36.10 (CH-cHx), 50.27 (CH-ala), 66.05 [O-CH₂(CH₂)₂], 127.36 (*o*-Ph, *p*-TSA), 130.24 (*m*-Ph, *p*-TSA), 142.13 (*ipso*-C-CH₃, *p*-TSA), 143.89 (*ipso*-C-S, *p*-TSA), 171.49 (C=O).

Phenyl(2-cyclohexyl ethoxy-L-alaninyl)phosphorochloridate

[0206]



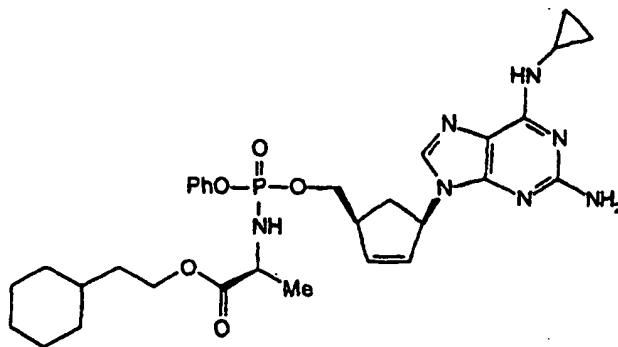
[0207] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.9 ml, 6.0 mmol), dry triethylamine (1.7 ml, 12.0 mmol), L-alanine (cyclohexyl ethyl) ester *p*-toluene sulfonate salt **12a** (2.24g, 6.0 mmol) and dry DCM (100 ml total). The crude product was obtained as a clear, colourless oil (1.86 g, 83 %).

δ_P (CDCl₃, 121 MHz) 8.96, 9.31

The product was redissolved in dry THF (5 ml) and used as a 0.372 g/ml solution.

(1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(2-cyclohexyl-1-ethoxy-L-alaninyl)]phosphate [Cf 1780]

[0208]



[0209] Prepared according to **Standard Procedure 4**, from (1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ¹BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(cyclohexyl ethoxy-L-alaninyl) phosphorochloridate **12b** (2.1 ml of 0.372 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 2.5 hrs. The crude residue was purified twice by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to an off-white foam after trituration and coevaporation with diethyl ether (0.302 g, 0.5 mmol, 69 %).

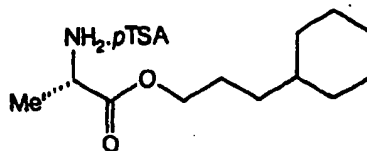
δ_P (CDCl₃, 121 MHz) 3.91, 3.94; δ_H (CDCl₃, 300 MHz) 0.64 (m, 2H, CH₂-cPr), 0.91 (m, 4H, CH₂ and CH₂-cPr), 1.21 (m, 2H, CH₂), 1.41 (m, 3H, CH₃-ala), 1.52 (m, 2H, CH-cHx and 6'H₈), 1.70 (m, 6H, 3 × CH₂), 2.80 (m, 1H, 6'H₈), 3.04 (m, 1H, CH-cPr), 3.18 (m, 1H, 4'H), 4.10 (m, 6H, NH-ala, CH-ala, OCH₂ and 5'H), 5.03 (bs, 1H, NH₂), 5.56 (m, 1H, 1'H), 5.96 (m, 1H, 3'H), 5.98 (m, 1H, NH-cPr), 6.10 (m, 1H, 2'H), 7.25 (m, 5H, Ar), 7.51 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 6.35 (CH₂-cPr), 20.05, 20.12 (CH₃-ala), 22.69 (CH-cPr), 25.11 (CH₂), 25.37 (CH₂), 32.04, 32.07 (6'C), 33.45, 33.58 (CH-cHx), 34.76 (CH₂), 44.58, 44.69 (4'C), 49.28 (CH-ala), 57.78, 57.83 (1'C), 62.88 (OCH₂), 67.86 (5'C), 113.82 (5C), 119.10-119.19 (*p*-Ph), 123.85 (*o*-Ph), 128.61 (*m*-Ph), 130.12 (3'C), 134.44, 134.54 (8C), 135.28, 135.38 (2'C),

EP 1 117 669 B1

149.66-149.94 (6C and *ipso*-Ph), 155.28 (4C), 155.99 (2C), 172.57, 172.66 (C=O).

L-Alanine (3-cyclohexyl-1-propyl) ester *p*-toluene sulfonate salt

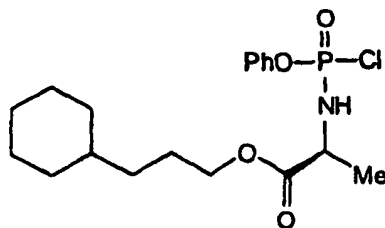
[0210]



[0211] Prepared according to **Standard Procedure 2**, from L-alanine (1.0 g, 11 mmol), *p*-TSA monohydrate (2.35 g, 12 mmol), 3-cyclohexyl-1-propanol (1.7 ml, 11 mmol) and toluene (65 ml). The solvent was removed and diethyl ether was added. The resulting suspension was filtered to give the product as a white solid (3.9 g, 10.1 mmol, 90 %). δ_H (d_4 -CH₃OH, 300 MHz) 0.92 (m, 2H, CH₂), 1.23 (m, 6H, 3 \times CH₂), 1.54 (d, 3H, CH₃-ala, J = 7), 1.71 (m, 7H, CH-cHx and 3 \times CH₂), 2.39 (s, 3H, CH₃, *p*-TSA), 4.10 (q, 1H, CH-ala, J = 7), 4.22 (m, 2H, O-CH₂), 7.25 (d, 2H, ArH, *p*-TSA), 7.72 (d, 2H, ArH, *p*-TSA); δ_C (d_4 -CH₃OH, 75 MHz) 16.66 (CH₃-ala), 21.74 (CH₃-*p*TSA), 27.36 (CH₂), 27.83 (CH₂), 28.11 (CH₂), 34.80 (CH₂), 34.90 (CH₂), 39.03 (CH-cHx), 50.27 (CH-ala), 68.27 (OCH₂), 127.36 (*o*-Ph, *p*-TSA), 130.24 (*m*-Ph, *p*-TSA), 142.12 (*ipso*-C-CH₃, *p*-TSA), 143.89 (*ipso*-C-S, *p*-TSA), 171.49 (C=O).

Phenyl(3-cyclohexyl-1-propoxy-L-alaninyl)phosphorochloridate

[0212]



[0213] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.9 ml, 6.0 mmol), dry triethylamine (1.7 ml, 12.0 mmol), L-alanine (3-cyclohexyl-1-propyl) ester *p*-toluene sulfonate salt **13a** (2.32g, 6.0 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, pale yellow oil (2.31 g, 99 %).

δ_P (CDCl₃, 121 MHz) 8.99, 9.35

[0214] The product was redissolved in dry THF (5 ml) and used as a 0.463 g/ml solution.

EP 1 117 669 B1

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(3-cyclohexyl-1-propoxy-L-alaninyl)]phosphate [Cf 1781]

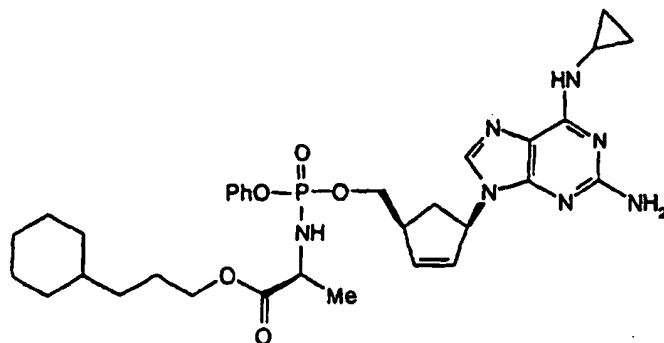
[0215]

5

10

15

20



25

30

35

[0216] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^tBuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(3-cyclohexyl-1-propoxy-L-alaninyl) phosphorochloridate **13b** (1.8 ml of 0.463 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 2.5 hrs. The crude residue was purified by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to an off-white foam after trituration and coevaporation with diethyl ether (0.276 g, 0.4 mmol, 62 %).

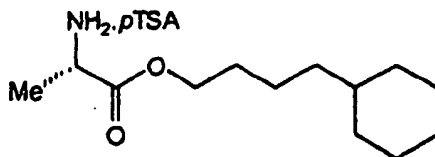
δ_P (CDCl₃, 121 MHz) 3.89, 3.91; δ_H (CDCl₃, 300 MHz) 0.64 (m, 2H, CH₂-cPr), 0.89 (m, 2H, CH₂-cPr), 1.21 (m, 6H, 3 × CH₂), 1.41 (m, 3H, CH₃-ala), 1.66 (m, 8H, CH-cHx, 3 × CH₂ and 6'H_a), 2.81 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.18 (m, 1H, 4'H), 4.04 (m, 6H, NH-ala, CH-ala, OCH₂ and 5'H), 4.98 (bs, 1H, NH₂), 5.56 (m, 1H, 1'H), 5.91 (m, 1H, 3'H and NH-cPr), 6.11 (m, 1H, 2'H), 7.26 (m, 5H, Ar), 7.57 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 6.37 (CH₂-cPr), 20.09, 20.15 (CH₃-ala), 22.66 (CH-cPr), 24.85 (CH₂), 25.27 (CH₂), 25.55 (CH₂), 29.92 (CH₂), 32.20, 32.33 (6'C), 33.49, 33.57 (CH-cHx), 36.22 (CH₂), 44.58, 44.68 (4'C), 49.27 (CH-ala), 57.78, 57.83 (1'C), 65.01 (OCH₂), 67.84 (5'C), 113.86 (5C), 119.10-119.19 (*p*-Ph), 123.85 (*o*-Ph), 128.61 (*m*-Ph), 130.12 (3'C), 134.47, 134.57 (8C), 135.28, 135.38 (2'C), 149.65-149.74 (6C and *ipso*-Ph), 155.27 (4C), 158.96 (2C), 172.53, 172.64 (C=O).

L-Alanine (4-cyclohexyl-1-butyl) ester p-toluene sulfonate salt

[0217]

40

45



50

55

[0218] Prepared according to **Standard Procedure 2**, from L-alanine (0.51 g, 5.8 mmol), *p*-TSA monohydrate (1.21 g, 6.3 mmol), 4-cyclohexyl-1-butanol (1.0 ml, 5.8 mmol) and toluene (65 ml). The *p*-toluene sulfonate salt was obtained as a white crystalline solid (2.15 g, 5.4 mmol, 93 %).

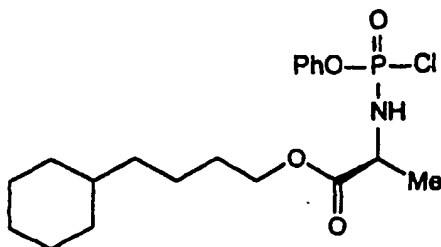
δ_H (*d*₄-CH₃OH, 300 MHz) 0.92 (m, 2H, CH₂), 1.17 (m, 6H, 3 × CH₂), 1.39 (m, 2H, CH₂), 1.54 (d, 3H, CH₃-ala, *J* = 7), 1.69 (m, 7H, CH-cHx and 3 × CH₂), 2.39 (s, 3H, CH₃, *p*-TSA), 4.10 (q, 1H, CH-ala, *J* = 7), 4.24 (m, 2H, O-CH₂), 7.25 (d, 2H, ArH, *p*-TSA), 7.72 (d, 2H, ArH, *p*-TSA); δ_C (*d*₄-CH₃OH, 75 MHz) 16.66 (CH₃-ala), 21.74 (CH₃-*p*-TSA), 24.51 (CH₂), 27.89 (CH₂), 28.18 (CH₂), 30.25 (CH₂), 34.90 (CH₂), 38.59 (CH₂), 39.27 (CH-cHx), 50.27 (CH-ala), 67.94 (OCH₂), 127.36 (*o*-Ph, *p*-TSA), 130.23 (*m*-Ph, *p*-TSA), 142.15 (*ipso*-C-CH₃, *p*-TSA), 143.89 (*ipso*-C-

EP 1 117 669 B1

S, *p*-TSA), 171.49 (C=O).

Phenyl(4-cyclohexyl-1-butoxy-L-alaninyl)phosphorochloridate

[0219]



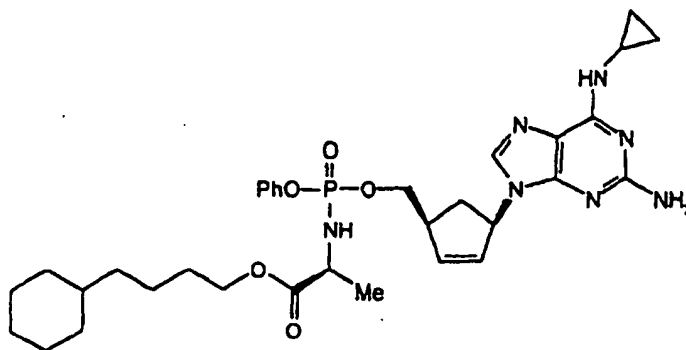
[0220] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.45 ml, 3.0 mmol), dry triethylamine (0.8 ml, 6.0 mmol), L-alanine (4-cyclohexyl-1-butyl) ester *p*-toluene sulfonate salt **14a** (1.2g, 3.0 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, brown oil (1.36 g, >100 %).

δ_P (CDCl₃, 121 MHz) 8.91, 9.28

The product was redissolved in dry THF (5 ml) and used as a 0.272 g/ml solution.

(1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(4-cyclohexyl-1-butoxy-L-alaninyl)]phosphate [Cf 1782]

[0221]



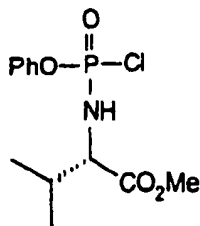
[0222] Prepared according to **Standard Procedure 4**, from (1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^tBuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(3-cyclohexyl-1-propoxy-L-alaninyl) phosphorochloridate **14b** (3.1 ml of 0.272 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in CNCl₃) showed the reaction to be complete after 2.5 hrs. The crude residue was purified twice by column chromatography, using MeOH:CHCl₃ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to an off-white foam after trituration and coevaporation with diethyl ether (0.341 g, 0.5 mmol, 75 %).

δ_P (CDCl₃, 121 MHz) 3.89, 3.91; δ_H (CDCl₃, 300 MHz) 0.65 (m, 2H, CH₂-cPr), 0.86 (m, 2H, CH₂-cPr), 1.21 (m, 8H, 4 × CH₂), 1.41 (m, 3H, CH₃-ala), 1.65 (m, 8H, CH-cHx, 3 × CH₂ and 6'H_a), 2.81 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.19 (m, 1H, 4'H), 4.04 (m, 6H, NH-ala, CH-ala, OCH₂ and 5'H), 4.96 (bs, 1H, NH₂), 5.56 (m, 1H, 1'H), 5.92 (m, 1H, 3'H and NH-cPr), 6.11 (m, 1H, 2'H), 7.26 (m, 5H, Ar), 7.52 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 6.37 (CH₂-cPr), 20.10, 20.16 (CH₃-ala), 22.00 (CH₂), 22.65 (CH-cPr), 25.34 (CH₂), 25.64 (CH₂), 27.77 (CH₂), 32.28 (CH-cHx), 33.48, 33.56 (6'C), 36.45 (CH₂), 44.58, 44.68 (4'C), 49.24 (CH-ala), 57.79, 57.84 (1'C), 64.69 (OCH₂), 67.84, 67.94 (5'C), 113.86 (5C), 119.10-119.19 (*p*-Ph), 123.86 (*o*-Ph), 128.62 (*m*-Ph), 130.11, 130.17 (3'C), 134.47, 134.57 (8C), 135.28, 135.39 (2'C), 149.65-149.74 (6C and *ipso*-Ph), 155.26 (4C), 158.96 (2C), 172.54, 172.64 (C=O).

EP 1 117 669 B1

Phenyl(methoxy-L-valinyl)phosphorochloridate

[0223]



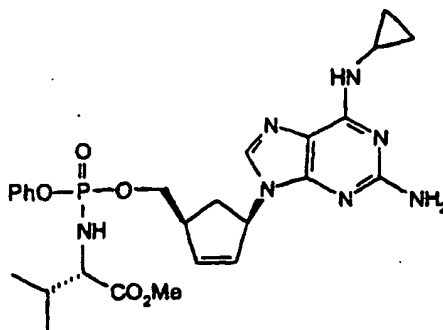
[0224] Prepared according to Standard Procedure 3, from phenyl dichlorophosphate (0.45 ml, 3.0 mmol), dry triethylamine (0.8 ml, 6.0 mmol), L-valine methyl ester hydrochloride salt (0.5 g, 3.0 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, colourless oil (0.922 g, >100 %).

δ_P (CDCl₃, 121 MHz) 8.99, 9.37

[0225] The product was redissolved in dry THF (5 ml) and used as a 0.184 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(methoxy-L-valinyl)phosphate] [Cf 1686]

[0226]



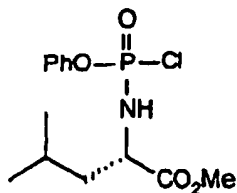
[0227] Prepared according to Standard Procedure 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^tBuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol), phenyl(methoxy valinyl) phosphorochloridate **15a** (3.5 ml of 0.184 g/ml solution, 2.1 mmol) and dry THF (5 ml). The reaction mixture was stirred for 16 hrs, after which time a further 1.5 ml of the solution of **15a** was added. The reaction mixture was stirred for a further 4 hrs. The crude residue was purified by column chromatography, using MeOH:DCM (5:95) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.161 g, 0.3 mmol, 41 %).

δ_P (CDCl₃, 121 MHz) 4.65, 4.74; δ_H (CDCl₃, 300 MHz) 0.66 (m, 2H, CH₂-cPr), 0.94 [m, 8H, CH₂-cPr and CH(CH₃)₂], 1.71 (m, 1H, 6'H_a), 2.06 [m, 1H, CH(CH₃)₂], 2.81 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.18 (m, 1H, 4'H), 3.52 (m, 1H, CH-val), 3.70 (d, 3H, OCH₃), 3.83 (m, 1H, NH-val), 4.22 (m, 2H, 5'H), 4.86 (bs, 2H, NH₂), 5.56 (m, 1H, 1'H), 5.74 (bs, 1H, NH-cPr), 5.93 (m, 1H, 3'H), 6.11 (m, 1H, 2'H), 7.27 (m, 5H, ArH), 7.52 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 6.37 (CH₂-cPr), 16.36, 16.45 [CH(CH₃)₂], 22.65 (CH-cPr), 31.08, 31.16 [CH(CH₃)₂], 33.61 (6'C), 44.60, 44.70 (4'C), 51.05, 51.10 (OCH₃), 57.78 (1'C), 58.96, 59.01 (CH-val), 67.90 (5'C), 113.91 (5C), 119.03-119.13 (o-Ph), 123.80 (p-Ph), 128.58 (m-Ph), 130.05, 130.14 (3'C), 134.47 (8C), 135.27, 135.39 (2'C), 149.66-149.84 (6C and ipso-Ph), 155.28 (4C), 158.96 (2C), 172.10, 172.19 (C=O); *m/z* (FAB) 556.2428 (MH⁺, C₂₆H₃₅N₇O₅P requires 556.2437).

EP 1 117 669 B1

Phenyl(metboxy-L-leucinyl)phosphorochloridate

[0228]



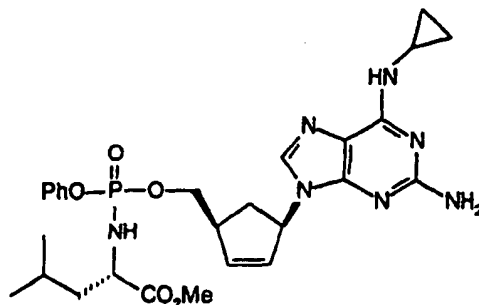
[0229] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.41 ml, 2.8 mmol), dry triethylamine (0.77 ml, 5.5 mmol), L-leucine methyl ester hydrochloride salt (0.5 g, 2.8 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, pale yellow oil (1.062 g, >100 %).

δ_P (CDCl₃, 121 MHz) 9.33, 9.51

[0230] The product was redissolved in dry THF (5 ml) and used as a 0.212 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(methoxy-L-leucinyl)phosphate] [Cf 1718]

[0231]



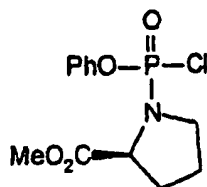
[0232] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol 0.2 g, 0.7 mmol), ^tBuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol), phenyl (methoxy-L-leucinyl) phosphoro- chloridate **16a** (3.2 ml of 0.212 g/ml solution, 2.1 mmol) and dry THE (10 ml). TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 2 hrs. The crude residue was purified twice by column chromatography, using MeOH: CHCl₃ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.211 g, 0.4 mmol, 53 %).

δ_P (CDCl₃, 121 MHz) 3.98, 4.06; δ_H (CDCl₃, 300 MHz) 0.64 (m, 2H, CH₂-cPr), 0.89 [m, 8H, CH₂-cPr and CH(CH₃)₂], 1.51 (m, 2H, CH₂-leu), 1.69 [(m, 2H, CH(CH₃)₂ and 6'H_a), 2.80 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.16 (m, 1H, 4'H), 3.67 (m, 1H, CH-leu), 3.69 (d, 3H, OCH₃), 3.98 (m, 1H, NH-leu), 4.19 (m, 2H, 5'H), 4.97 (bs, 2H, NH₂), 5.55 (m, 1H, 1'H), 5.91 (m, 1H, NH-cPr and 3'H), 6.09 (m, 1H, 2'H), 7.25 (m, 5H, ArH), 7.51 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 6.37 (CH₂-cPr), 20.69, 20.82 (CH₃-leu), 22.69 (CH-cPr), 23.28, 23.41 [CH(CH₃)₂], 33.54 (6'C), 42.60-42.81 (CH₂-leu), 44.59, 44.70 (4'C), 51.19, (OCH₃), 52.07, 52.16 (CH-leu), 57.80 (1'C), 67.91, 67.98 (5'C), 113.88 (5C), 118.99-119.14 (o-Ph), 123.80 (p-Ph), 128.58 (m-Ph), 130.06, 130.14 (3'C), 134.53 (8C), 135.27, 135.34 (2'C), 149.68-149.76 (6C and *lps*-Ph), 155.28 (4C), 158.97 (2C), 173.12, 173.23 (C=O); *m/z* (FAB) 570.2610 (MH⁺, C₂₇H₃₇N₇O₅P requires 570.2594).

EP 1 117 669 B1

Phenyl(methoxy-L-prolinyl)phosphorochloridate

[0233]



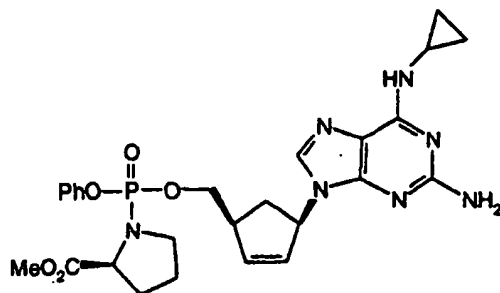
[0234] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.54 ml, 3.6 mmol), dry triethylamine (1.0 ml, 7.2 mmol), L-proline methyl ester hydrochloride salt (0.6 g, 3.6 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, colourless oil (1.24 g, >100 %).

δ_P (CDCl₃, 121 MHz) 9.02, 9.22

[0235] The product was redissolved in dry THF (5 ml) and used as a 0.248 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(methoxy-L-prolinyl)phosphate [Cf 1719]

[0236]



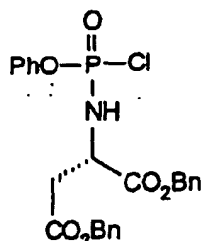
[0237] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^tBuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol), phenyl(methoxy-L-prolinyl)phosphorochloridate 17a (2.6 ml of 0.248 g/ml solution, 2.1 mmol) and dry THF (10 ml). TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 20 hrs. The crude residue was purified twice by column chromatography, using MeOH: CHCl₃ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.168 g, 0.3 mmol, 44 %).

δ_P (CDCl₃, 121 MHz) 2.83, 2.90; δ_H (CDCl₃, 300 MHz) 0.65 (m, 2H, CH₂-cPr), 0.90 (m, 2H, CH₂-cPr), 1.92 (m, 5H, CH₂CH₂-pro and 6'H_B), 2.83 (m, 1H, 6'H_B), 3.04 (m, 1H, CH-cPr), 3.17 (m, 1H, 4'H), 3.45 (m, 2H, N-CH₂-pro), 3.70 (d, 3H, OCH₃), 4.13 (m, 1H, CH-pro), 4.30 (m, 2H, 5'H), 4.87 (bs, 2H, NH₂), 5.56 (m, 1H, 1'H), 5.73 (bs, 1H, NH-cPr), 5.91 (m, 1H, 3'H), 6.12 (m, 1H, 2'H), 7.27 (m, 5H, ArH), 7.55 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 6.42 (CH₂-cPr), 22.62 (CH-cPr), 23.91, 24.02 (CH₂-pro), 30.38, 30.49 (CH₂-pro), 33.54 (6'C), 44.61, 44.72 (4'C), 46.89 (N-CH₂), 51.07, 51.19 (OCH₃), 57.71, 57.80 (1'C), 58.84, 58.92 (CH-pro), 67.67, 67.75 (5'C), 113.87 (5C), 118.90-119.22 (o-Ph), 123.64, 123.73 (p-Ph), 128.55, 128.59 (m-Ph), 130.00 (3'C), 134.46 (8C), 135.42, 135.63 (2'C), 149.81, 149.90 (6C and *lps*-Ph), 155.20 (4C), 158.87 (2C), 172.72, 173.23 (C=O); *m/z* (FAB) 554.2283 (MH⁺, C₂₆H₃₃N₇O₅P requires 554.2281).

EP 1 117 669 B1

Phenyl(dibenzoyloxy-L-aspartinyl)phosphorochloridate

[0238]



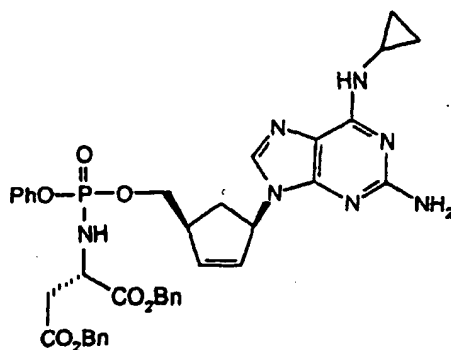
[0239] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.45 ml, 3.0 mmol), dry triethylamine (0.8 ml, 6.0 mmol), L-aspartate dibenzyl ester *p*-toluene sulfonate salt (1.46 g, 3.0 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, yellow oil (0.8024 g, 55 %).

δ_P (CDCl₃, 121 MHz) 9.43, 9.58

[0240] The product was redissolved in dry THF (5 ml) and used as a 0.16 g/ml solution.

(1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(dibenzoyloxy-L-aspartinyl)phosphate] [Cf 1720]

[0241]



[0242] Prepared according to **Standard Procedure 4**, from (1*S*,4*R*)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.157 g, 0.55 mmol), ^tBuMgCl (1.0 M in THF: 1.1 ml, 1.1 mmol), phenyl(dibenzoyloxy-L-aspartinyl) phosphorochloridate 18a (5.0 ml of 0.16 g/ml solution, 1.6 mmol) and dry THF (10 ml). TLC (8 % MeOH in CHCl₃) showed the reaction to be complete after 1.5 hrs. The crude residue was purified twice by column chromatography, using MeOH: CHCl₃ (3:97) as eluent, to give the product as a clear, colourless oil, which solidified to an off-white foam after trituration and coevaporation with diethyl ether (0.284 g, 0.4 mmol, 70 %).

δ_P (CDCl₃, 121 MHz) 3.68, 4.24; δ_H (CDCl₃, 300 MHz) 0.63 (m, 2H, CH₂-cPr), 0.85 (m, 2H, CH₂-cPr), 1.63 (m, 1H, 6'H_B), 2.71 (m, 1H, 6'H_B), 3.06 (m, 2H, CH-cPr and 4'H), 4.14 (m, 2H, CH-asp, NH-asp), 4.34 (m, 2H, 5'H), 4.98 (bs, 2H, NH₂), 5.06 (d, 2H, OCH₂Ph), 5.13 (d, 2H, OCH₂Ph), 5.53 (m, 1H, 1'H), 5.88 (m, 2H, NH-cPr and 3'H), 6.01 (m, 1H, 2'H), 7.25 (m, 15H, ArH), 7.49 (d, 1H, 8H); δ_C (CDCl₃, 75 MHz) 6.35 (CH₂-cPr), 22.64 (CH-cPr), 33.40 (6'C), 37.44, 37.60 (CH₂-asp), 44.50, 44.57 (4'C), 50.20, 50.33 (CH-asp), 57.79 (1'C), 65.77 (OCH₂Ph), 66.65 (OCH₂Ph), 67.86, 68.00 (5'C), 113.85 (5C), 119.09-119.34 (o-Ph), 123.92 (p-Ph), 127.34-127.55 (m-Ph and m/p-Bn), 128.61 (o-Bn), 130.06 (3'C), 134.00 (ipso-Bn), 134.03 (ipso-Bn), 134.61 (8C), 135.23, 135.27 (2'C), 149.47-149.91 (6C and ipso-Ph), 155.28 (4C), 158.95 (2C), 169.22, 169.43, 170.00, 170.29 (C=O).

EP 1 117 669 B1

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl (2-methylpropyl)oxy-L-alaninyl phosphate) CF1672

[0243] This was prepared by Standard Procedure 4. 70% yield.

δ_p 3.87, 3.91.

δ_H 0.64 (2H, m, CH_2H_b , CH_2H_b , cyclopropyl), 0.92 (8H, m, CH_2H_b , CH_2H_b , cyclopropyl, $CH(CH_3)_2$), 1.42 (3H, m, CH_3 alaninyl), 1.71 (1H, m, $6'-H_aH_b$), 1.92 (1H, m, $CH(CH_3)_2$), 2.81 (1H, m, $6'-H_aH_b$), 3.03 (1H, m, CH cyclopropyl), 3.19 (1H, m, $4'-H$), 3.87 (3H, m, CH alaninyl, $CH_2CH(CH_3)_2$), 4.09 (1H, m, NH alaninyl), 4.20 (2H, m, $5'-H$), 4.91 (2H, br s, NH_2), 5.53 (1H, br m, $1'-H$), 5.80 (1H, br s, NH-cyclopropyl), 5.92 (1H, m, $3'-H$), 6.12 (1H, m, $2'-H$), 7.31 (5H, m, Ph-H), 7.48 (1H, br d, 8H)

δ_C 5.45 (CH_2 -cyclopropyl x 2), 17.01 ($CH(CH_3)_2$), 19.23, 19.29 (Me alaninyl), 21.74 (CH-cyclopropyl), 25.72 ($CH(CH_3)_2$), 32.58, 32.64 ($6'-C$), 43.66, 43.76 ($4'-C$), 48.35 (CH alaninyl), 56.90 ($1'-C$), 66.88, 66.96, 67.03 ($5'-C$), 69.57, 69.60 ($CH_2CH(CH_3)_2$), 118.17, 118.20, 118.24, 118.27 (α -Ph, $5-C$), 122.94 (ρ -Ph), 127.70 (m -Ph), 129.19, 129.24 ($3-C$), 134.35, 134.45 ($8-C$, $2'-C$), 148.81, 148.72 (i -Ph), 149.62, 149.76 ($6-C$), 154.34 ($4-C$), 158.91, 158.96 ($2-C$), 171.68, 171.58 (C(O) alaninyl).

MS m/e 570.2505 (M^+ , $C_{27}H_{36}N_7O_5P$ requires 570.2515).

HPLC t_R 33.11 min (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl (2,2-dimethylpropyl)oxy-L-alaninyl phosphate) CF1673

[0244] This was prepared by Standard Procedure 4. 94% yield.

δ_p 3.88, 3.94.

δ_H 0.61 (2H, m, CH_2H_b , CH_2H_b , cyclopropyl), 0.85 (2H, br m, CH_2H_b , CH_2H_b , cyclopropyl), 0.91 (9H, s, $C(CH_3)_3$), 1.41 (3H, m, CH_3 alaninyl), 1.70 (1H, m, $6'-H_aH_b$), 2.78 (1H, m, $6'-H_aH_b$), 3.03 (1H, m, CH cyclopropyl), 3.18 (1H, m, $4'-H$), 3.81 (3H, m, CH alaninyl, $CH_2CH(CH_3)_2$), 4.09 (1H, m, NH alaninyl), 4.20 (2H, m, $5'-H$), 4.97 (2H, br s, NH_2), 5.52 (1H, br m, $1'-H$), 5.86 (1H, br s, NH-cyclopropyl, $3'-H$), 6.08 (1H, m, $2'-H$), 7.25 (5H, m, Ph-H), 7.48 (1H, br d, 8H).

δ_C 7.89 (CH_2 -cyclopropyl x 2), 21.74, 21.77 (Me alaninyl), 26.81 ($C(CH_3)_3$), 24.21 (CH-cyclopropyl), 31.90 ($C(CH_3)_3$), 35.06 ($6'-C$), 46.10, 46.20 ($4'-C$), 50.79, 50.83 (CH alaninyl), 59.42 ($1'-C$), 66.35 ($5'-C$), 69.34, 69.41, 69.49 ($CH_2C(CH_3)_3$), 116.41 ($5-C$), 120.62, 120.66, 120.68, 120.72 (α -Ph), 125.39 (ρ -Ph), 130.15 (m -Ph), 131.61, 131.65 ($3'-C$), 136.82, 136.90 ($8-C$, $2'-C$), 151.16, 151.25 ($6-C$, i -Ph), 156.78 ($4-C$), 158.91, 160.44 ($2-C$), 174.09, 174.20 (C(O) alaninyl).

ES+ m/e 584.2640 (MH^+ , $C_{28}H_{38}N_7O_5P$ requires 584.2672).

HPLC t_R 34.97 min (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl (3-methylbutyl)oxy-L-alaninyl phosphate) CF1674

[0245] This was prepared by Standard Procedure 4. 4.47% yield.

δ_p 3.87, 3.89:

δ_H 0.57 (2H, m, CH_2H_b , CH_2H_b , cyclopropyl), 0.80 (8H, m, CH_2H_b , CH_2H_b , cyclopropyl, $CH(CH_3)_2$), 1.30 (3H, m, CH_3 alaninyl), 1.42 (2H, m, OCH_2CH_2), 1.62 (2H, m, $6'-H_aH_b$, $CH(CH_3)_2$), 2.70 (1H, m, $6'-H_aH_b$), 2.92 (1H, br s, CH cyclopropyl), 3.07 (1H, m, $4'-H$), 3.88 (3H, m, CH alaninyl, OCH_2CH_2), 4.07 (3H, m, NH alaninyl, $5'-H$), 4.91 (2H, br s, NH_2), 5.48 (1H, br m, $1'-H$), 5.83 (2H, br s, NH-cyclopropyl, $3'-H$), 6.03 (1H, m, $2'-H$), 7.18 (5H, m, Ph-H), 7.42 (1H, br d, 8H).

δ_C 7.81 (CH_2 -cyclopropyl x 2), 21.49, 21.56 (Me alaninyl), 22.79, 22.83 ($CH(CH_3)_2$), 24.10 ($CH(CH_3)_2$), 25.38 (CH-cyclopropyl), 34.91, 34.99 (OCH_2CH_2), 37.54 ($6'-C$), 46.01, 46.11 ($4'-C$), 50.70 (CH alaninyl), 59.25, 59.29 ($1'-C$), 64.63, 64.66 (OCH_2CH_2), 69.22, 69.30, 69.38 ($5'-C$), 116.17 ($5-C$), 120.53, 120.55, 120.59, 120.61 (α -Ph), 125.28 (ρ -Ph), 130.05 (m -Ph), 131.54, 131.60 ($3'-C$), 135.96 ($8-C$), 136.70, 136.81 ($2'-C$), 151.09, 151.17 ($6-C$, i -Ph), 156.68 ($4-C$), 160.34 ($2-C$), 173.94, 174.05 (C(O) alaninyl).

ES+ m/e 584.2664 (MH^+ , $C_{28}H_{38}N_7O_5P$ requires 584.2672).

HPLC t_R 38.51 min (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl (cycloheptanyl)oxy-L-alaninyl phosphate) CF1752

[0246] This was prepared by Standard Procedure 4. 4.41% yield. δ_p 3.96, 3.98.

δ_H 0.68 (2H, m, CH_2H_b , CH_2H_b , cyclopropyl), 0.99 (2H, m, CH_2H_b , CH_2H_b , cyclopropyl), 1.36 (5H, m, CH_3 alaninyl, $5''-H_aH_b$, $6''-H_aH_b$), 1.80 (11H, m, $6'-H_aH_b$, $2''-H$, $3''-H$, $4''-H$, $7''-H$, $5''-H_aH_b$, $6''-H_aH_b$), 2.80 (1H, m, $6'-H_aH_b$), 3.12 (1H,

EP 1 117 669 B1

- br s, CH cyclopropyl), 3.22 (1H, m, 4'-H), 3.97 (2H, m, CH alaninyl, NH alaninyl), 4.20 (2H, m, 5'-H), 4.95 (1H, m, O-CH), 5.18 (2H, br s, NH₂), 5.57 (1H, br m, 1'-H), 5.90 (1H, m, 3'-H), 6.12 (1H, m, 2'-H), 6.25 (1H, br s, NH cyclopropyl), 7.25 (5H, m, Ph-H), 7.51 (1H, br d, 8H).
- δ_C 15.08 (CH₂-cyclopropyl x 2), 28.76, 28.82 (Me alaninyl), 30.40, 30.44 (3"-C, 6"-C), 24.10 (CH(CH₃)₂), 31.57 (CH-cyclopropyl), 35.87 (4'-C, 5"-C), 41.26, 41.29, 41.31, 41.36 (6'-C), 42.24 (2"-C, 7"-C), 53.32, 53.42 (4'-C), 58.08 (CH alaninyl), 61.15 (1'-C), 66.62 (5'-C), 116.17 (5-C), 127.81, 127.85, 127.88, 127.91 (o-Ph), 132.54 (p-Ph), 137.32, 137.49 (m-Ph), 138.75 (3'-C), 143.21 (8-C), 144.13, 144.22 (2'-C), 158.40, 158.49 (6-C, i-Ph), 164.42 (4-C), 167.41 (2-C), 180.47, 180.51, 180.59 (C(O) alaninyl).
- ES+ m/e 632.2719 (M[Na]⁺, C₃₀H₄₀N₇O₅NaP requires 632.2726).
- HPLC t_R 41.92 min (0% CH₃CN (0 min), 80% CH₃CN (35 min), 80% CH₃CN (45 min), 0% CH₃CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl diethoxy-L-aspartyl phosphate) CF1714

- [0247] This was prepared by Standard Procedure 4.54% yield.
- δ_P 3.76, 4.19.
- δ_H 0.62 (2H, m, CH_aH_b, CH_aH_b, cyclopropyl), 0.88 (2H, m, CH_aH_b, CH_aH_b, cyclopropyl), 1.25 (6H, m, CH₃-CH₂-O aspartyl x 2), 1.68 (1H, m, 6'-H_aH_b), 2.75 (2H, m, -(CO)-CH_aH_b aspartyl, 6'-H_aH_b), 2.97 (2H, m, CH cyclopropyl, -(CO)-CH_aH_b aspartyl), 3.16 (1H, m, 4'-H), 4.15 (8H, m, CH aspartyl, CH₂-O aspartyl x 2, NH aspartyl, 5'-H), 4.90 (2H, br s, NH₂), 5.52 (1H, br m, 1'-H), 5.80 (1H, br s, NH-cyclopropyl), 5.90 (1H, m, 3'-H), 6.08 (1H, m, 2'-H), 7.21 (5H, m, Ph-H), 7.48 (1H, br d, 8H).
- δ_C 8.65 (CH₂-cyclopropyl x 2), 15.31 (CH₃-CH₂-O aspartyl x 2), 24.92 (CH-cyclopropyl), 35.72 ((CO)-CH₂ aspartyl), 39.74, 39.91 (6'-C), 46.82, 46.90 (4'-C), 52.41, 52.47 (CH aspartyl), 60.11 (1'-C), 62.22 (CH₃-CH₂-O(CO)CH₂ aspartyl), 63.15 (CH₃-CH₂-O(CO)CH aspartyl), 70.14, 70.27, 70.35 (5'-C), 116.12 (5-C), 121.33, 121.40, 121.49, 121.55 (o-Ph), 126.15 (p-Ph), 130.86 (m-Ph), 132.36 (3'-C), 136.90 (8-C), 137.54 (2'-C), 151.81, 151.85 (6-C, i-Ph), 157.39 (4-C), 161.01 (2-C), 171.67, 171.81 (C(O)CH₂ aspartyl), 172.38, 172.48, 172.52, 172.62 (C(O) aspartyl).
- ES+ m/e 614.2393 (MH⁺, C₂₈H₃₇N₇O₇P requires 614.2492).
- HPLC t_R 30.37 min (0% CH₃CN (0 min), 80% CH₃CN (35 min), 80% CH₃CN (45 min), 0% CH₃CN (55 min)).

- (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-methionyl phosphate) CF1715**

- [0248] This was prepared by Standard Procedure 4.49% yield.
- δ_P 3.90, 4.03.
- δ_H 0.61 (2H, m, CH_aH_b, CH_aH_b, cyclopropyl), 0.86 (2H, m, CH_aH_b, CH_aH_b, cyclopropyl), 1.71 (1H, m, CH-CH_aCH_b methioninyl), 1.90 (1H, m, CH-CH_aCH_b methioninyl), 2.01 (3H, d, CH₃-S-), 2.30 (1H, m, 6'-H_aH_b), 2.47 (2H, m, 5'-CH₂), 2.78 (1H, m, 6'-H_aH_b), 2.97 (1H, br m, CH cyclopropyl), 3.14 (1H, m, 4'-H), 3.70 (3H, d, CH₃-O-), 3.80 (1H, m, CH methioninyl), 4.17 (3H, m, NH methioninyl, 5'-H), 4.89 (2H, br s, NH₂), 5.49 (1H, m, 1'-H), 5.80 (1H, br s, NH-cyclopropyl), 5.90 (1H, m, 3'-H), 6.08 (1H, m, 2'-H), 7.24 (5H, m, Ph-H), 7.43 (1H, br d, 8H).
- δ_C 6.52 (CH₂-cyclopropyl x 2), 14.42, 14.47 (CH₃-S-), 22.81 (CH-cyclopropyl), 28.63, 28.78 (S-CH₂), 32.62, 32.73, 32.81 (CH-CH₂- methioninyl), 33.65 (6'-C), 44.73, 44.83 (4'-C), 51.67 (CH methioninyl), 57.99 (1'-C), 68.13, 68.20, 68.27 (5'-C), 114.03 (5-C), 119.15, 119.22, 119.24, 119.30 (o-Ph), 124.05, 124.10 (p-Ph), 128.80 (m-Ph), 130.26, 130.30 (3'-C), 134.72 (8-C), 135.42, 135.47 (2'-C), 149.76, 149.80, 149.84, 149.89 (i-Ph), 150.08 (6-C), 155.38 (4-C), 159.06 (2-C), 172.25, 172.28, 172.32, 172.36 (C(O)).
- ES+ m/e 588.2053 (MH⁺, C₂₆H₃₄N₇O₅PS requires 588.2080).
- HPLC t_R 29.64 min (0% CH₃CN (0 min), 80% CH₃CN (35 min), 80% CH₃CN (45 min), 0% CH₃CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-tryptophanyl phosphate) CF1750

- [0249] This was prepared by Standard Procedure 4.70% yield.
- δ_P 3.88, 4.01.
- δ_H 0.68 (2H, m, CH_aH_b, CH_aH_b, cyclopropyl), 0.92 (2H, m, CH_aH_b, CH_aH_b, cyclopropyl), 1.53 (1H, m, 6'-H_aH_b), 2.68 (1H, m, 6'-H_aH_b), 2.99 (2H, br m, CH cyclopropyl, 4'-H), 3.22 (2H, m, CH₂-Trp), 3.66 (3H, d, CH₃-O-), 3.93 (3H, m, NH Trp, 5'-H), 4.35 (1H, m, CH Trp), 4.94 (2H, br s, NH₂), 5.49 (1H, m, 1'-H), 5.87 (2H, m, NH-cyclopropyl, 3'-H), 5.97 (1H, m, 2'-H), 7.01 (1H, m, 6'-H), 7.26 (7H, m, Ph-H, 4"-H, 5"-H), 7.46 (1H, m, 7"-H), 7.52 (1H, m, 2"-H), 8.63 (1H, br d, 8H).
- δ_C 7.81 (CH₂-cyclopropyl x 2), 24.10 (CH-cyclopropyl), 34.86, 34.91 (6'-C), 45.81, 45.90, 46.00 (4'-C), 52.97 (CH Trp), 59.24, 59.29 (1'-C), 69.14, 69.20 (5'-C), 109.86, 110.11 (3"-C), 111.72 (7"-C), 118.91 (5-C), 119.95, 120.04 (4"-C, 5"-C),

EP 1 117 669 B1

120.40, 120.47, 120.57, 120.63 (*o*-Ph), 122.49, 122.56 (6"-H), 123.70 (2"-C), 125.23, 125.29 (*p*-Ph), 127.79, 127.98 (9"-C), 130.04 (*m*-Ph), 131.27 (3'-C), 136.08 (8-C), 136.50, 136.55, 136.76, 136.87 (2'-C, 8"-C), 151.05, 151.14, 151.17, 151.26 (*i*-Ph, 6-C), 156.68 (4-C), 160.35 (2-C), 173.58, 173.66 (C(O)).

ES+ *m/e* 643.2432 (MH⁺, C₃₂H₃₆N₈O₅P requires 643.2546).

5 HPLC *t_R* 31.46 min (0% CH₃CN (0 min), 80% CH₃CN (35 min), 80% CH₃CN (45 min), 0% CH₃CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-isoleuciny) phosphate) CF1751

10 [0250] This was prepared by Standard Procedure 4.60% yield.

δ_p 4.48, 4.54.

δ_H 0.68 (2H, m, CH₂H_b, CH₂H_b, cyclopropyl), 0.91 (8H, m, CH₂H_b, CH₂H_b, cyclopropyl, CH₃ x 2 isoleuciny), 1.15 (1H, m, CH₂CH₂ isoleuciny), 1.45 (1H, m, CH₂CH₂ isoleuciny), 1.75 (2H, m, 6'-H_aH_b, CH₃CH), 2.83 (1H, m, 6'-H_aH_b), 3.05 (1H, br m, CH cyclopropyl), 3.19 (1H, m, 4'-H), 3.62 (1H, m, NH isoleuciny), 3.71 (3H, d, CH₃-O-), 3.88 (1H, m, CH isoleuciny), 4.21 (2H, m, 5'-H), 4.91 (2H, br s, NH₂), 5.55 (1H, m, 1'-H), 5.81 (1H, br s, NH-cyclopropyl), 5.93 (1H, m, 3'-H), 6.12 (1H, m, 2'-H), 7.28 (5H, m, Ph-H). 7.52 (1H, br d, 8H).

15 δ_C 7.82 (CH₂-cyclopropyl x 2), 11.89 (CH₃CH₂), 15.72 (CH₃CH), 24.08 (CH-cyclopropyl), 25.04, 25.13 (CH₃CH₂), 34.99 (6'-C), 39.49, 39.56, 39.64 (CH₂CH), 46.04, 46.14 (4'-C), 52.46, 52.50 (CH isoleuciny), 59.24, 59.44, 59.54 (1'-C), 69.34 (5'-C), 116.12 (5-C), 120.47, 120.53, 120.58 (*o*-Ph), 125.27 (*p*-Ph), 130.03 (*m*-Ph), 131.50, 131.57 (3'-C), 136.04 (8-C), 136.84, 136.74 (2'-C), 151.10, 151.18, 151.27 (*i*-Ph, 6-C), 156.69 (4-C), 161.06, 161.09, 161.35, 161.41 (2-C), 173.48, 173.53 (C(O)).

20 ES+ *m/e* 570.2496 (MH⁺, C₂₇H₃₇N₇O₅P requires 570.2594).

HPLC *t_R* 32.83, 33.14 min (0% CH₃CN (0 min), 80% CH₃CN (35 min), 80% CH₃CN (45 min), 0% CH₃CN (55 min)).

25 **(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl dimethoxy-L-glutamyl phosphate) CF1749**

[0251] This was prepared by Standard Procedure 4.38% yield.

δ_p 3.99.

30 δ_H 0.68 (2H, m, CH₂H_b, CH₂H_b, cyclopropyl), 0.91 (2H, m, CH₂H_b, CH₂H_b, cyclopropyl), 1.73 (1H, m, 6'-H_aH_b), 2.12 (1H, m, C(O)CH₂CH₂H_b), 2.38 (2H, m, C(O)CH₂), 2.82 (1H, m, 6'-H_aH_b), 3.05 (1H, m, CH cyclopropyl), 3.18 (1H, m, 4'-H), 3.68 (3H, s, MeOC(O)CH₂), 3.72 (3H, s, MeOC(O)CH), 3.85 (1H, m, NH glutyl), 4.10 (1H, m, CH glutyl), 4.21 (2H, m, 5'-H), 4.95 (2H, br s, NH₂), 5.57 (1H, br m, 1'-H), 5.88 (1H, br s, NH-cyclopropyl), 5.95 (1H, m, 3'-H), 6.10 (1H, m, 2'-H), 7.25 (5H, in, Ph-H), 7.54 (1H, br s, 8H).

35 δ_C 7.82 (CH₂-cyclopropyl x 2), 24.12 (CH-cyclopropyl), 29.66, 29.73, 29.88 (C(O)CH₂CH₂), C(O)CH₂CH₂, 34.91 (6'-C), 46.02, 46.12 (4'-C), 52.19 (CH₃OC(O)CH₂CH₂), 54.17, 54.28 (CH₃OC(O)CH₂), 54.17 (CH glutyl), 59.31 (1'-C), 69.50 (5'-C), 115.42 (5-C), 120.48, 120.51, 120.55, 120.58 (*o*-Ph), 125.39 (*p*-Ph), 130.09, 130.22 (*m*-Ph), 131.55, 131.60 (3'-C), 136.13 (8-C), 136.68, 136.77 (2'-C), 150.98, 151.05, 151.13 (6-C), 151.76 (*i*-Ph), 156.65 (4-C), 160.99, 161.02, 161.08, 161.12 (2-C), 173.33, 173.43 (C(O) x 2 glutyl).

40 ES+ *m/e* 600.2216 (MH⁺, C₂₇H₃₅N₇O₇P requires 600.2335).

HPLC *t_R* 27.25 min (0% CH₃CN (0 min), 80% CH₃CN (35 min), 80% CH₃CN (45 min), 0% CH₃CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl (methoxy- α -ethyl-L-glyciny) phosphate) CF1783

45 [0252] This was prepared by Standard Procedure 4.44% yield.

δ_p 4.10.

50 δ_H 0.59 (2H, m, CH₂H_b, CH₂H_b, cyclopropyl), 0.83 (5H, br m, CH₂H_b, CH₂H_b, cyclopropyl, CH₃-CH₂), 1.68 (3H, m, CH₃-CH₂, 6'-H_a), 2.69 (1H, m, 6'-H_aH_b), 2.91 (1H, m, 4'-H), 3.06 (1H, m, CH cyclopropyl), 3.58 (3H, d, J 3.0, MeO), 3.90 (2H, m, NH glyciny, CH glyciny), 4.07 (2H, m, 5'-H), 5.02 (2H, br s, NH₂), 5.42 (1H, m, 1'-H), 5.75 (1H, m, 3'-H), 5.98 (1H, m, 2'-H), 6.03 (1H, m, NH cyclopropyl), 7.18 (5H, m, Ph-H), 7.41 (1H, br d, 8H).

55 δ_C 7.76 (CH₂-cyclopropyl x 2), 9.68, 9.76 (CH₃CH₂), 24.12 (CH-cyclopropyl), 28.05 (CH₃CH₂), 35.01 (6'-C), 46.02, 46.13 (4'-C), 52.70, 52.73 (CH₃O), 56.02 (1'-C), 59.25 (CH-ala), 69.38 (5'-C), 116.10 (5-C), 120.48, 120.50, 120.55, 120.57 (*o*-Ph), 125.27 (*p*-Ph), 130.04 (*m*-Ph), 131.51 (3'-C), 135.86 (8-C), 136.86 (2'-C), 151.08, 151.13, 151.22 (6-C, *i*-Ph), 156.67 (4-C), 160.40 (2-C), 173.84, 173.87, 173.92 (C(O) alaniny).

ES+ *m/e* 564.2094 (M[Na]⁺, C₂₅H₃₂N₇O₅NaP requires 564.2100).

HPLC *t_R* 16.82, 16.84 min (0% CH₃CN (0 min), 80% CH₃CN (15 min), 80% CH₃CN (25 min), 0% CH₃CN (35 min)).

EP 1 117 669 B1

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl (methoxy- α -phenyl(RS)glycyl) phosphate) CF1784

[0253] This was prepared by Standard Procedure 4.46% yield.

δ_p 3.18, 3.28, 3.42, 4.29.

Proton and Carbon NMR gave complex spectra, consistent with the racemised product.

ES+ m/e 612.2086 ($M[Na]^+$, $C_{29}H_{32}N_7O_5NaP$ requires 612.2100).

HPLC t_R 17.63, 18.50 min (0% CH_3CN (0 min), 80% CH_3CN (15 min), 80% CH_3CN (25 min), 0% CH_3CN (35 min)). (1:1.08 racemisation by HPLC)

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl (methoxy- α -butyl-L-glydnyl phosphate) CF1786

[0254] This was prepared by Standard Procedure 4.51% yield*.

δ_p 4.10, 4.16.

δ_H 0.51 (2H, m, CH_aH_b , CH_aH_b , cyclopropyl), 0.72 (5H, br m, CH_aH_b , CH_aH_b , cyclopropyl, CH_3-CH_2), 1.18 (4H, m, $CH_3-CH_2-CH_2$), 1.54 (3H, m, CH_2-CH_2-O , 6'- H_aH_b), 2.73 (1H, m, 6'- H_aH_b), 2.93 (1H, m, 4'-H), 3.09 (1H, m, CH cyclopropyl), 3.52 (1H, m, CH glycyl), 3.62 (3H, s, MeO), 3.87 (1H, m, NH glycyl), 4.12 (2H, m, 5'-H), 4.75 (2H, br s, NH_2), 5.45 (1H, m, 1'-H), 5.79 (2H, br s, NH-cyclopropyl, 3'-H), 6.00 (1H, m, 2'-H), 7.20 (5H, m, Ph-H), 7.42 (1H, br d, 8H). δ_C 7.76 (CH_2 -cyclopropyl x 2), 14.23 (CH_3CH_2), 22.56 (CH_3CH_2), 24.14 (CH-cyclopropyl), 27.43, 27.50 ($CH_3CH_2CH_2$), 34.50, 34.58 (CH_2CH_2O), 35.01 (6'-C), 46.02, 46.12 (4'-C), 52.66, 52.68 (CH_3O), 54.87, 54.94 (1'-C), 59.20 (CH-ala), 69.30, 69.37 (5'-C), 115.18 (5-C), 120.29, 120.42, 120.50, 120.57 (α -Ph), 125.21 (ρ -Ph), 130.00 (m -Ph), 131.51, 131.54 (3'-C), 135.86 (8-C), 136.71, 136.76 (2'-C), 151.12, 151.16, 151.20, 151.25 (6-C, ρ -Ph), 156.73 (4-C), 160.49, 160.96 (2-C), 174.19, 174.26 (C(O) glycyl).

ES+ m/e 592.2428 ($M[Na]^+$, $C_{27}H_{36}N_7O_5NaP$ requires 592.2413).

HPLC t_R 18.34, 18.41, min and 16.64 min (6:1) (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).

* Note: compound isolated as 6:1 (S:R) stereoisomeric mixture at the amino acid residue α -carbon. Additional resonances in the ^{31}P NMR spectra are noted at 4.35 and 5.18, corresponding to the minor configuration (R) amino acid residue containing diastereoisomers.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl (methoxy- α -propyl-L-glycyl) phosphate) CF1785

[0255] This was prepared by Standard Procedure 4.50% yield.

δ_p 4.14, 4.21.

δ_H 0.62 (2H, m, CH_aH_b , CH_aH_b , cyclopropyl), 0.86 (5H, br m, CH_aH_b , CH_aH_b , cyclopropyl, CH_3-CH_2), 1.32 (2H, m, CH_3-CH_2), 1.63 (3H, m, CH_3-CH_2 , 6'- H_aH_b), 2.79 (1H, m, 6'- H_aH_b), 3.03 (1H, m, 4'-H), 3.18 (1H, m, CH cyclopropyl), 3.71 (3H, d, J 3.0, MeO), 3.97 (1H, m, CH glycyl), 4.15 (3H, m, 5'-H, NH glycyl), 5.09 (2H, br s, NH_2), 5.55 (1H, m, 1'-H), 5.90 (1H, m, 3'-H), 6.08 (2H, m, 2'-H, NH cyclopropyl), 7.23 (5H, m, Ph-H), 7.52 (1H, br d, 8H).

δ_C 7.55 (CH_2 -cyclopropyl x 2), 13.98 (CH_3CH_2), 18.62, 18.70 (CH_3CH_2), 24.15 (CH-cyclopropyl), 35.00 (6'-C), 36.89, 36.96 (CH_2CH_2O), 46.02, 46.12 (4'-C), 52.68 (CH_3O), 54.70, 54.77 (1'-C), 59.21 (CH-ala), 69.31, 69.38 (5'-C), 115.24 (5-C), 120.45, 120.51, 120.57 (α -Ph), 125.22 (ρ -Ph), 130.01 (m -Ph), 131.54 (3'-C), 135.89 (8-C), 136.72, 136.78 (2'-C), 151.11, 151.16, 151.20, 151.25 (6-C, ρ -Ph), 156.72 (4-C), 160.45, 160.95 (2-C), 174.18, 174.25 (C(O) alaninyl).

ES+ m/e 578.2259 ($M[Na]^+$, $C_{26}H_{34}N_7O_5NaP$ requires 578.2257).

HPLC t_R 17.57 min (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-((ρ -(2'',2''-dimethoxypropionic acid methyl ester)-phenyl)methoxy-L-alaninyl phosphate) CF1671

[0256] This was prepared by Standard Procedure 4.24 % yield.

δ_p 3.72, 3.84.

δ_H 0.56 (2H, m, CH_aH_b , CH_aH_b , cyclopropyl), 0.79 (2H, m, CH_aH_b , CH_aH_b , cyclopropyl), 1.30 (3H, m, CH_3 alaninyl), 1.63 (1H, m, 6'- H_aH_b), 2.70 (1H, m, 6'- H_aH_b), 2.95 (1H, br s, 4'-H), 3.07 (3H, m, CH cyclopropyl, Ph- CH_2), 3.26 (6H, s, (OMe) $_2$), 3.52 (3H, s, C(OMe) $_2$ COOMe), 3.61 (3H, s, COOMe alaninyl), 3.84 - 4.08 (4H, m, CH alaninyl, NH alaninyl, 5'-H), 4.99 (2H, br s, NH_2), 5.46 (1H, br m, 1'-H), 5.81 (1H, br s, 3'-H), 6.02 (2H, m, 3'-H, NH-cyclopropyl), 6.02 (1H, m, 2'-H), 7.02 (4H, m, Ph-H), 7.45 (1H, br d, 8H).

δ_C 7.77 (CH_2 -cyclopropyl x 2), 21.37 (Me alaninyl), 24.01 (CH-cyclopropyl), 34.89 (6'-C), 39.55 (Ph- CH_2), 45.97, 46.09

EP 1 117 669 B1

(4'-C), 50.53 ((MeO)₂, CH₃OO alaninyl), 52.65 (C(OMe)₂COOMe), 59.28 (1'-C), 69.29 (5'-C), 103.27 (C(OMe)₂), 120.31, 120.38 (o-Ph), 122.94 (p-Ph), 131.35 (m-Ph), 131.39 (3'-C), 136.79 (8-C, 2'-C), 150.14, 150.05 (i-Ph, 6-C), 152.12 (4-C), 160.24 (2-C), 169.08 (C(OMe)₂COOMe), 174.36, 174.46 (C(O) alaninyl).
ES+ m/e 696.2531 ([M]⁺, C₃₀H₄₀N₇O₉NaP requires 696.2523).

5 HPLC t_R 29.02 min (0% CH₃CN (0 min), 80% CH₃CN (35 min), 80% CH₃CN (45 min), 0% CH₃CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-((p-methoxyphenyl) methoxy-L-alaninyl phosphate) CF1815

10 [0257] This was prepared by Standard Procedure 4.23% yield.

δ_P 4.23, 4.28.

δ_H 0.72 (2H, m, CH₂H_b, CH₂H_b, cyclopropyl), 1.0 (2H, m, CH₂H_b, CH₂H_b, cyclopropyl), 1.48 (3H, m, CH₃ alaninyl), 1.82 (1H, m, 6'-H_aH_b), 2.80 (1H, m, 6'-H_aH_b), 3.11 (1H, br s, 4'-H), 3.25 (1H, m, CH cyclopropyl), 3.67 (1H, m, NH alaninyl), 3.77 (3H, s, COOMe alaninyl), 3.89 (3H, s, MeO-Ar), 4.14 (1H, m, CH alaninyl), 4.30 (2H, m, 5'-H), 4.94 (2H, br s, NH₂), 5.65 (1H, br m, 1'-H), 5.83 (1H, br s, NH-cyclopropyl), 6.00 (1H, m, 3'-H), 6.17 (1H, m, 2'-H), 6.92 (2H, m, m-Ar), 7.23 (2H, m, o-Ar), 7.63 (1H, s, 8H).

15 δ_C 7.81 (CH₂-cyclopropyl x 2), 21.46, 21.52 (Me alaninyl), 24.00 (CH-cyclopropyl), 34.96 (6'-C), 46.04, 46.14 (4'-C), 50.64 (CH₃OO alaninyl), 52.89 (CH-alaninyl), 56.02 (CH₃O-Ar), 59.28 (1'-C), 69.30 (5'-C), 114.98 (m-Ph, 5-C), 121.42, 121.46, 121.52 (o-Ph), 131.52, 131.56 (3'-C), 135.98, (2'-C), 136.76, 136.87 (i-Ph), 144.61 (8-C), 156.71 (4-C), 157.01 (p-Ar), 161.40, 160.99 (2-C), 174.39, 174.50 (C(O) alaninyl).

20 HPLC t_R 16.28 (0% CH₃CN (0 min), 80% CH₃CN (15 min), 80% CH₃CN (25 min), 0% CH₃CN (35 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-((p-propoxyphenyl) methoxy-L-alaninyl phosphate) CF1816

25

[0258] This was prepared by Standard Procedure 4.56% yield.

δ_P 4.33, 4.41.

30 δ_H 0.62 (2H, m, CH₂H_b, CH₂H_b, cyclopropyl), 0.82 (2H, m, CH₂H_b, CH₂H_b, cyclopropyl), 1.03 (3H, t, J 6.0, CH₃-CH₂), 1.39 (3H, m, CH₃ alaninyl), 1.66 (1H, m, 6'-H_aH_b), 1.80 (2H, h, J 6.0, CH₃-CH₂), 2.79 (1H, m, 6'-H_aH_b), 3.01 (1H, br s, 4'-H), 3.12 (1H, m, CH cyclopropyl), 3.72 (3H, s, COOMe alaninyl), 3.89 (2H, t, J 6.0, CH₂-O), 4.04 (2H, m, CH alaninyl, NH alaninyl), 4.17 (2H, m, 5'-H), 5.10 (2H, br s, NH₂), 5.52 (1H, br m, 1'-H), 5.51 (1H, br s, NH-cyclopropyl), 5.89 (1H, m, 3'-H), 6.04 (1H, m, 2'-H), 6.81 (2H, m, m-Ar), 7.11 (2H, m, o-Ar), 7.51 (1H, s, 8H).

35 δ_C 7.77 (CH₂-cyclopropyl x 2), 10.91 (CH₃-CH₂), 21.39, 21.46 (Me alaninyl), 22.97 (CH₃-CH₂), 24.14 (CH-cyclopropyl), 34.96 (6'-C), 46.02, 46.13 (4'-C), 50.57, 50.65 (CH₃OO alaninyl), 52.85, 52.87 (CH-alaninyl), 53.89 o, 59.25 (1'-C), 69.16, 69.24, 69.33 (5'-C), 70.30 (CH₂-O), 115.24, 115.26 (5-C), 115.57 (m-Ph), 121.37, 121.40, 121.43, 121.46 (o-Ph), 131.51, 131.57 (3'-C), 135.93, (2'-C), 136.77, 136.85 (i-Ph), 144.47, 144.55 (8-C), 156.54, 156.73 (4-C), 160.45 (p-Ar), 160.91 (2-C), 174.48, 174.59 (C(O) alaninyl).

HPLC t_R min (0% CH₃CN (0 min), 80% CH₃CN (15 min), 80% CH₃CN (25 min), 0% CH₃CN (35 min)).

40

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[4-hydroxyacetophenone-(methoxy-L-alaninyl)]-phosphoramidate Cf 1794

[0259] This was prepared by Standard procedure 4. The crude residue was purified twice by column chromatography, using MeOH:CHCl₃ (3%:97) and MeOH:EtOAc (5:95) as eluent, to give the product as a white foam (30 mg, 17 mmol, 15 %).

45

δ_P 3.496.

50 δ_H 0.66 (m, 2H, CH₂-cPr), 0.85 (m, 2H, CH₂-cPr), 1.33 (m, 3H, CH₃-CH), 1.7 (m, 1H, H'6), 2.53 (s, 3H, CH₃-COPh), 2.8 (m, 1H, H'6), 2.9 (m, 1H, CH-cPr), 3.1 (m, 1H, H'4), 3.6 (s, 3H, CH₃-O), 3.9 (m, 1H, CH₃-CH), 4.1 (m, 2H, H'5), 4.9 (m, 2H, NH₂), 5.5 (m, 1H, H'1), 5.85 (m, 1H, H'3), 6.1 (m, 2H, H'2, NHcPr) 7.2 (dd, 2H, o-Ar), 7.5 (m, 1H, H8), 7.8 (dd, 2H, p-Ar)

δ_C 6.371 (CH₂cPr), 20 (CH-CH₃aa), 21.671 (NHCH₃), 25 (CH₃CO), 33.458 (C6), 44.55 (C'4), 49.5 (CHaa), 51.4 (OCH₃), 57.9 (C'1), 67.9 (C'5), 113.787 (C5), 120 (o-Ar), 122.22 (p-Ar), 128.743 (m-Ar), 130 (C'3), 134.53 (C'2), 135.31 (C8), 150.31 (i-Ar), 155.18 (C6), 156.342 (C2), 158.8 (C4), 173.004 (COOCH₃), 198 (CO-Ar).

HPLC t_R: 15.976 min (0% CH₃CN (0 min), 80% CH₃CN (15 min), 80% CH₃CN (25 min), 0% CH₃CN (35 min)).

55

EP 1 117 669 B1

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[4n-butylphenyl-(methoxy-L-alaninyl)]-phosphate Cf 1795

- [0260]** The crude residue was purified twice by column chromatography, using MeOH:CHCl₃ (3%:97) and MeOH:CH₂Cl₂ (5:95) as eluent, to give the product as a white foam (15 mg, 0.025 mmol, 4 %),
 δ_p 3.93-4.00.
 δ_H 0.66 (m, 2H, CH₂-cPr), 0.85 (m, 2H, CH₂-cPr), 1.1 (m, 3H, CH₃-CH₂), 1.2 (m, 4H, CH₂-CH₂), 1.33 (m, 3H, CR₃-CR), 1.7 (m, 1H, H'6), 2.5 (m, 2H, CH₂-Ar), 2.8 (m, 1H, H'6), 2.9 (m, 1H, CH-cPr), 3.1 (m, 1H, H'4), 3.6 (s, 3H, CH₃-O), 3.9 (m, 1H, CH₃-CH), 4.1 (m, 2H, H'5), 4.9 (m, 2H, NH₂), 5.5 (m, 1H, H'1), 5.85 (m, 1H, H'3), 6.1 (m, 2H, H'2, NHcPr), 7.2 (dd, 2H, *o*-Ar), 7.5 (m, 1H, H₈), 7.8 (dd, 2H, *p*-Ar).
 δ_C 6.371 (CH₂cPr), 14.345 (CH₃-CH₂), 21.49 (CH-CH₃aa), 22.66 (CH₂-CH₃), 21.671 (NHCH₃), 30.127 (CH₂-CH₂-CH₂), 33.458 (C'6), 34.047 (CH₂-Ar), 44.55 (C'4), 49.5 (CHaa), 51.4 (OCH₃), 57.9 (C'1), 67.9 (C5), 113.787 (C5), 120 (*o*-Ar), 122.22 (*p*-Ar), 128.743 (*m*-Ar), 130 (C'3), 134.53 (C'2), 135.31 (C8), 146.58 (*i*-Ar), 155.18 (C6), 156.342 (C2), 158.8 (C4), 173.004 (COOCH₃)
 HPLC t_r : 19.591 min (0% CH₃CN (0 min), 80% CH₃CN (15 min), 80% CH₃CN (25 min), 0% CH₃CN (35 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenylphenyl-(methoxy-L-alaninyl)]-phosphate Cf 1788

- [0261]** The crude residue was purified three times by column chromatography, using MeOH:CHCl₃ (3:97) and MeOH:CH₂Cl₂ (5:95) and MeOH:AcOEt (3:97) as eluent, to give the product as a yellow foam (35 mg, 0.058 mmol, 8 %).
 δ_p 3.94-3.96.
 δ_H 0.66 (m, 2H, CH₂-cPr), 0.85 (m, 2H, CH₂-cPr), 1.33 (m, 3H, CH₃-CH), 1.7 (m, 1H, H'6), 2.8 (m, 1H, H'6), 2.9 (m, 1H, CH-cPr), 3.25 (m, 1H, H'4), 3.6 (s, 3H, CH₃-O), 4.1 (m, 1H, CH₃-CH), 4.25 (m, 2H, H'5), 4.9 (m, 2H, NH₂), 5.5 (m, 1H, H'1), 5.85 (m, 1H, H'3), 6.15 (m, 2H, H'2, NHcPr), 7.35 (m, 9H, Ar), 7.6 (m, 1H, H₈).
 δ_C 6.371 (CH₂cPr), 21.49 (CH-CH₃aa), 21.671 (NHCH₃), 33.458 (C'6), 46.14 (C'4), 50.671 (CHaa), 52.9 (OCH₃), 59.9 (C'1), 65.9 (C'5), 115.787 (C5), 120 (*o*-Ar), 122.22 (*p*-Ar), 128.743 (*m*-Ar), 130 (C'3), 134.53 (C'2), 135.31 (C8), 145.25 (*i*-Ar), 155.18 (C6), 156.342 (C2), 158.8 (C4), 173.004 (COOCH₃).
 HPLC t_r : 19.147 min (0% CH₃CN (0 min), 80% CH₃CN (15 min), 80% CH₃CN (25 min), 0% CH₃CN (35 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenoxyphenyl-(methoxy-L-alaninyl)]-phosphate Cf 1787

- [0262]** The crude residue was purified twice by column chromatography, using MeOH:CHCl₃ (3:97) and MeOH:CH₂Cl₂ (5:95) as eluent, to give the product as a yellow foam (35 mg, 0.058 mmol, 8 %).
 δ_p 4.212-4.184.
 δ_H 0.66 (m, 2H, CH₂-cPr), 0.85 (m, 2H, CH₂-cPr), 1.33 (m, 3H, CH₃-CH), 1.7 (m, 1H, H'6), 2.8 (m, 1H, H'6), 2.9 (m, 1H, CH-cPr), 3.25 (m, 1H, H'4), 3.6 (s, 3H, CH₃-O), 4.1 (m, 1H, CH₃-CH), 4.25 (m, 2H, H'5), 4.9 (m, 2H, NH₂), 5.5 (m, 1H, H'1), 5.85 (m, 1H, H'3), 6.15 (m, 2H, H'2, NHcPr), 7.35 (m, 9H, Ar), 7.6 (m, 1H, H₈).
 δ_C 6.371 (CH₂cPr), 21.49 (CH-CH₃aa), 21.671 (NHCH₃), 33.458 (C'6), 46.14 (C'4), 50.671 (CHaa), 52.9 (OCH₃), 59.9 (C'1), 65.9 (C'5), 115.787 (C5), 120 (*o*-Ar), 122.22 (*p*-Ar₂), 128.743 (*m*-Ar), 130 (C'3), 134.53 (C'2), 135.31 (C8), 153.83 (*i*-Ar₂, *m*-Ar₁), 155.18 (C6), 156.342 (C2), 158.8 (C4), 173.004 (COOCH₃).
 HPLC t_r : 18.830 min (0% CH₃CN (0 min), 80% CH₃CN (15 min), 80% CH₃CN (25 min), 0% CH₃CN (35 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl methoxy- α , α -cyclopentylglycyl] phosphate Cf1763

- [0263]** This was prepared by Standard procedure 4 in 77% yield.
 ^{31}P (CDCl₃) 3.02, 3.09
 ^1H (CDCl₃) 0.56-0.61 (2H, m, CH₂ (cpro)), 0.81-0.89 (2H, m, CH₂ (cpro)), 1.58-1.78 (5H, m, CCH₂CH₂CH₂CH₂C, and H₆'), 1.87-2.18 (4H, m, CCH₂CH₂CH₂CH₂C), 2.64-2.74 (1H, m, H₆'), 2.83-3.09 (2H, m, CH(cpro), H₄'), 3.60-3.62 (3H, s, OCH₃(ala)), 4.04-4.19 (2H, m, H₅'), 5.20 (2H, bs, NH₂), 5.42-5.47 (1H, m, H₁'), 5.77-5.83 (1H, m, H₃'), 5.98-6.02 (1H, m, H₂'), 6.20 (NH(cpro)), 7.06-7.27 (5H, m, Ar), 7.42-7.48 (1H, s, H₈).
 ^{13}C (CDCl₃) 8.02 (CH₂(cpro)), 24.37, 24.41 (CCH₂CH₂CH₂CH₂C), 34.73 (C'6), 38.48, 38.68, 38.79, 38.87 (CCH₂CH₂CH₂CH₂C), 46.05, 46.15 (C'4), 52.99 (OCH₃(ala)), 59.56, 59.60 (C'1), 67.16 (C (aa), 69.28, 69.37 (C'5), 114.76 (C5), 120.46, 120.52 (*o*-Ph), 125.22 (*p*-Ph), 130.04 (*m*-Ph), 131.19 (C'3), 136.72 (C8), 137.13, 137.20 (C'2), 151.27, 151.31, 151.36, 151.40 (C6), 155.56 (C4), 158.95 (C2), 175.96, 176.00 (CO).

EP 1 117 669 B1

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl methoxy- α , α -cylohexylglycyl] phosphate Cf1764**[0264]** This was prepared by Standard procedure 4 in 15% yield.5 ³¹P (CDCl₃) 2.89, 3.00¹H (CDCl₃) 0.74 (2H, m, CH₂ (cpro)), 1.01-1.03 (2H, m, CH₂ (cpro)), 1.29-2.23 (11H, m, CCH₂CH₂CH₂CH₂CH₂C, and H₆'), 2.72-2.83 (1H, m, H₆'), 3.17 (1H, bs, CH(cpro)), 3.35-3.43 (1H, m, H₄'), 3.69-3.70 (3H, s, OCH₃(aa)), 4.16-4.29 (2H, m, H₅'), 5.52-5.66 (1H, m, H₁'), 5.79 (1H, bs, NH(cpro)), 5.85-5.90 (1H, m, H₃'), 6.08-6.10 (1H, m, H₂'), 7.15-7.35 (5H, m, Ar), 7.37-7.63 (1H, d, H₈).10 ¹³C (CDCl₃) 8.30 (CH₂(cpro)), 21.49, 21.68, 21.84, 22.02, 22.11 (CCH₂CH₂CH₂CH₂CH₂C), 25.14, 25.47, 25.72 (CCH₂CH₂CH₂CH₂CH₂C), 34.37, 34.59 (C₆'), 46.06, 46.16 (C₄'), 52.75, 53.12 (OCH₃(aa)), 59.95, 60.19 (C₁'), 69.22 (C₅'), 120.41, 120.47 (o-Ph), 125.22 (p-Ph), 130.04 (m-Ph), 130.72, 130.82 (C₃'), 137.41 (C₈), 137.56 (C₂'), 151.33, 151.43 (C₆), 175.37 (CO).15 **(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl methoxy- α , α -cyclopropylglycyl] phosphate Cf1762****[0265]** This was prepared by Standard procedure 4 in 69% yield.20 ³¹P (CDCl₃) 3.84¹H (CDCl₃) 0.68(2H, m, CH₂ (cpro)), 0.90-0.92 (2H, m, CH₂ (cpro)), 1.16-1.49 (4H, m, CCH₂CH₂C(aa)), 1.66-1.72 (1H, m, H₆'), 2.72-2.82 (1H, m, H₆'), 3.08-3.15 (2H, m, CH(cpro), H₄'), 3.61-3.63 (3H, d, OCH₃(aa)), 4.24-4.26 (2H, m, H₅'), 5.24 (2H, bs, NH₂), 5.53 (1H, bs, H₁'), 5.87(1H, m, H₃'), 6.07 (1H, m, H₂'), 6.42-6.45 (1H, bs, NH(cpro)), 7.15-7.35 (5H, m, Ar), 7.56-7.61 (1H, d, H₈).25 ¹³C (CDCl₃) 7.92 (CH₂(cpro)), 18.38 (CH₂ (aa)), 35.20 (C₆'), 52.88 (OCH₃(aa)), 59.45 (C₁'), 69.32 (C₅'), 120.52 (o-Ph), 125.29 (p-Ph), 130.04 (m-Ph), 137.03 (C₂'), 151.13 (C₆), 160.96, 160.98 (C₂), 174.35 (CO).**(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[p-(methoxycarbonyl) phenyl methoxy-L-alaninyl] phosphate Cf1766**30 **[0266]** This was prepared by Standard procedure 4 in 37% yield.³¹P (CDCl₃) 3.54, 3.5835 ¹H (CDCl₃) 0.66-0.69 (2H, m, CH₂ (cpro)), 0.88-0.94 (2H, m, CH₂ (cpro)), 1.38-1.43 (3H, t, CH₃(ala)), 1.70-1.81 (1H, m, H₆'), 2.76-2.89 (1H, m, H₆'), 3.07 (1H, m, CH(cpro)), 3.21 (1H, m, H₄'), 3.71-3.73 (3H, d, OCH₃(ala)), 3.94 (3H, s, COOCH₃), 3.98-4.12 (1H, m, CH(ala)), 4.20-4.31 (2H, m, H₅'), 5.19 (2H, bs, NH₂), 5.54-5.57 (1H, m, H₁'), 5.91-5.96 (1H, m, H₃'), 6.09-6.14 (1H, m, H₂'), 6.21 (1H, bs, NH(cpro)), 7.27-7.32 (2H, m, ArO, 2H), 7.53-7.54 (1H, d, H₈), 8.02-8.06 (2H, m, COAr, 2H).40 ¹³C (CDCl₃) 7.75 (CH₂(cpro)), 21.22, 21.29, 21.46 (CH₃(ala)), 24.16 (NHCH), 34.83 (C₆'), 45.97, 46.07 (C₄'), 50.59 (CH(ala)), 52.57, 59.32 (OCH₃ (ala), OCH₃(Ph)), 59.27, 59.32 (C₁'), 69.43 (C₅'), 115.07, 115.11 (C₅), 120.28, 120.31, 120.34, 120.38 (o-Ph), 127.07 (p-Ph), 131.58, 131.66 (m-Ph), 131.88 (C₃'), 135.94, 136.04 (C₂'), 136.61, 136.73 (C₈), 151.31 (C₆), 156.52 (C₂), 160.97 (C₄), 171.57 (CO), 174.30, 174.39 (CO).**(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[p-(trifluoromethylthio) phenyl methoxy-L-alaninyl] phosphate Cf 1769**45 **[0267]** This was prepared by Standard procedure 4 in 34% yield.³¹P (CDCl₃) 3.67, 3.8850 ¹H (CDCl₃) 0.81 (2H, bs, CH₂ (cpro)), 1.06-1.08 (2H, m, CH₂ (cpro)), 1.50-1.54 (3H, t, CH₃(ala)), 1.83-1.93 (1H, m, H₆'), 2.87-2.99 (1H, m, H₆'), 3.23-3.31 (1H, m, CH(cpro)), 3.82-3.84 (3H, d, OCH₃(ala)), 4.14-4.15 (1H, m, CH(ala)), 4.32-4.40 (2H, m, H₅'), 5.65 (3H, bs, H₁', NH₂), 6.01-6.04 (1H, m, H₃'), 6.19-6.23 (1H, m, H₂'), 6.64 (1H, bs, NH(cpro)), 7.37-7.43 (2H, m, Ar), 7.67 (1H, d, H₈), 7.73-7.76 (2H, m, Ar).¹³C (CDCl₃) 8.16 (CH₂(cpro)), 21.39, 21.45 (CH₃(ala)), 34.45 (C₆'), 46.09 (C₄'), 50.66 (CH(ala)), 53.01 (OCH₃ (ala)), 59.87 (C₁'), 69.34 (C₅'), 77.47, 77.67 (CF₃S ?), 121.64, 121.69 (o-Ph), 127.07 (p-Ph), 136.99, 137.14 (C₂'), 138.56 (C₈), 153.36, 153.45 (C₆), 160.93 (C₄), 174.27 (CO).55 **(1 S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[p-(2-methoxyvinyl) phenyl methoxy-L-alaninyl] phosphate Cf 1767****[0268]** This was prepared by Standard procedure 4 in 38% yield.

EP 1 117 669 B1

³¹P (CDCl₃) 3.70, 3.74

¹H (CDCl₃) 0.58-0.61 (2H, bs, CH₂ (cpro)), 0.81-0.85 (2H, m, CH₂ (cpro)), 1.30-1.36 (3H, t, CH₃(ala)), 1.61-1.72 (1H, m, H6'), 2.33 (3H, s, CH₃CO), 2.70-2.79 (1H, m, H6'), 2.99 (1H, bs, CH(cpro)), 3.13 (1H, bs, H4'), 3.64-3.65 (3H, d, OCH₃(ala)), 3.92-4.01 (1H, m, CH(ala)), 4.11-4.21 (2H, m, H5'), 5.14 (3H, bs, H1', NH₂), 5.47-5.49 (1H, m, H1'), 5.82-5.87 (1H, m, H3'), 6.01-6.06 (1H, m, H2'), 6.12 (1H, bs, NH(cpro)), 6.57-6.63 (1H, dd, CH₃COCH=CH), 7.14-7.46 (6H, m, H8, Ar, CH₃COCH=CH).

¹³C (CDCl₃) 7.95 (CH₂(cpro)), 21.45 (CH₃(ala)), 28.02 (CH₃CO), 34.69 (C6'), 46.11 (C4'), 50.64 (CH(ala)), 52.99 (OCH₃ (ala)), 59.53 (C1'), 121.03, 121.10, 121.17 (o-Ph), 127.39 (p-Ph), 130.13 (CH₃COCH=CH), 131.44, 131.55 (C3'), 136.76 (C2'), 142.59 (CH₃COCH=CH), 152.72 (C6), 174.26, 174.36 (CO(ala)), 198.70 (COCH₃).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[p-(2-phenylcarbonylvinyl)phenyl methoxy-L-alaninyl] phosphate Cf 1771

[0269] This was prepared by Standard procedure 4 in 26% yield.

³¹P (CDCl₃) 3.75, 3.79

¹H (CDCl₃) 0.61-0.66 (2H, m, CH₂ (cpro)), 0.85-0.91 (2H, m, CH₂ (cpro)), 1.39-1.44 (3H, m, CH₃(ala)), 1.67-1.86 (1H, m, H6'), 2.77-2.87 (1H, m, H6'), 3.04-3.05 (1H, bs, CH(cpro)), 3.19-3.21 (1H, bs, H4'), 3.72-3.73 (3H, d, OCH₃(ala)), 4.02-4.13 (1H, m, CH(ala)), 4.19-4.29 (2H, m, H5'), 5.17 (3H, bs, H1', NH₂), 5.53-5.58 (1H, m, H1'), 5.90-5.95 (1H, m, H3'), 6.09-6.15 (2H, m, H2', NH(cpro)), 7.24-8.08 (12H, m, Ar, CH=CH, Ar, H8).

¹³C (CDCl₃) 7.85 (CH₂(cpro)), 21.35, 21.41, 21.48 (CH₃(ala)), 24.22 (CH(NH)), 34.80 (C6'), 46.01 (C4'), 50.67 (CH (ala)), 52.97 (OCH₃ (ala)), 59.37 (C1'), 69.40 (C5'), 115.07 (C5), 121.01, 121.07, 121.14 (o-Ph), 128.92, 129.06 (p-Ph), 133.27 (C3'), 136.13, 136.23 (C2'), 138.53 (C8), 152.77, 152.86 (C6), 156.31 (C2), 160.97, 160.99 (C4), 174.31, 174.41 (CO(ala)), 190.76 (CO (Ar)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[p-(2,2-dicyanovinyl)phenyl methoxy-L-alaninyl] phosphate Cf 1768

[0270] This was prepared by Standard procedure 4 in 10% yield.

³¹P (CDCl₃) 4.54, 4.65

¹H (CDCl₃) 0.61-0.66 (2H, m, CH₂ (cpro)), 0.85-0.91 (2H, m, CH₂ (cpro)), 1.34-1.41 (3H, m, CH₃(ala)), 1.67-1.83 (1H, m, H6'), 2.77-2.88 (1H, m, H6'), 2.95-2.97 (1H, m, CH(cpro)), 3.23 (1H, bs, H4'), 3.68-3.70 (3H, d, OCH₃(ala)), 3.99-4.03 (1H, m, CH(ala)), 4.22-4.32 (2H, m, H5'), 5.49-5.53 (1H, m, H1'), 5.99-6.03 (1H, m, H3'), 6.16-6.22 (1H, m, H2'), 6.94-6.97 (1H, dd, Ar-CH=CH), 7.36-7.41 (Ar), 7.64-7.65 (1H, d, H8), 7.92-8.16 (Ar).

¹³C (CDCl₃) 6.56 (CH₂(cpro)), 19.85 (CH₃(ala)), 23.33 (CH(cpro)), 34.23 (C6'), 46.07 (C4'), 50.47, 50.53 (OCH₃ (ala)), 51.78 (CH(ala)), 59.51 (C1'), 69.19, 69.29 (C5'), 113.84, 114.08 (C5), 121.14, 121.21, 121.27 (o-Ph), 128.49 (p-Ph), 130.74, 130.85 (m-Ph), 132.84 (C3'), 136.01 (C2'), 136.88, 136.99 (C8), 156.47 (C2), 160.99, 161.03 (C4), 174.27 (CO).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[o-(carboxylate ethyl ester)phenyl methoxy-L-alaninyl] phosphate Cf 1798

[0271] This was prepared by Standard procedure 4 in 24% yield.

³¹P (CDCl₃) 4.03, 4.16

¹H (CDCl₃) 0.64-0.70 (2H, m, CH₂ (cpro)), 0.92-0.93 (2H, d, CH₂ (cpro)), 1.38-1.47 (6H, m, CH₃(ala), CH₃CH₂O), 1.73-1.83 (1H, m, H6'), 2.78-3.24 (3H, m, H6', H4', CH(cyclo)), 3.64-3.72 (3H, s, OCH₃(ala)), 4.08-4.20 (1H, m, CH (ala)), 4.23-4.45 (4H, m, H5', CH₂CH₃), 5.21 (2H, bs, NH₂), 5.55-5.60 (1H, m, H1'), 5.89-5.93 (1H, m, H3'), 6.13-6.18 (1H, m, H2'), 7.23-7.61 (1H, m, H8), 7.88-7.92 (1H, d, Ar).

¹³C (CDCl₃) 7.95 (CH₂(cpro)), 14.65 (CH₃CH₂), 21.33, 21.39, 21.68, 21.74 (CH₃(ala)), 24.30 (NHCH), 34.80 (C6'), 46.04, 46.14 (C4'), 50.49 (CH(ala)), 52.74, 52.83 (OCH₃ (ala)), 59.45 (C1'), 61.76, 61.82 (CH₂CH₃), 69.43, 69.51, 69.64 (C5'), 114.92 (C5), 122.93, 123.09, 123.60, 123.67, 125.26 (Ar), 131.34 (Ar), 131.77, 131.86 (C3'), 134.00 (Ar), 136.48 (C2'), 137.05 (C8), 150.20, 150.28 (C6), 155.88 (C2), 160.78, 160.86 (C4), 174.28, 174.39, 174.55, 174.65 (CO).

EP 1 117 669 B1

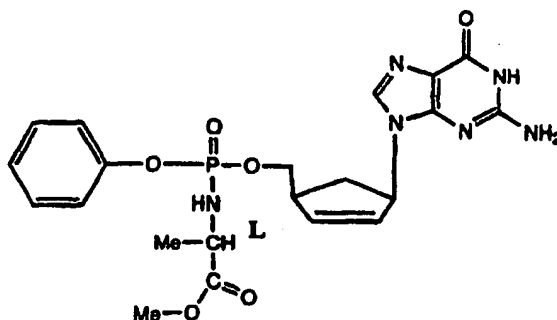
Example A

(1R, 4S)-9-[4-(hydroxymethyl)-2-cyclopenten-2-yl] guanine-5'-[phenyl-(methoxy-L-alaninyl)]-phosphate.

5 $C_{21}H_{25}O_6N_6P_1$, MW=488.45.

[0272] R. Vince and M. Hua, J. Med. Chem. 1990, 33, 17-21 describes a procedure for the synthesis of (1R,4S)-9-[4-(hydroxymethyl)-2-cyclopenten-1-yl] guanine. (1R,4S)-9-[4-(hydroxymethyl)-2-cyclopenten-1-yl] guanine (400mg, 1.618mmol) was dried by azeotrope with anhydrous pyridine (4x10ml), kept under $N_2(g)$, and suspended in anhydrous THE (30ml). $tBuMgCl$ (1.0M solution in THF) (1.6ml, 1.618mmol) was added dropwise and the resulting darker suspension vigorously stirred for 10mins. Phosphorochloridate (4.79ml, 2.43mmol) was added dropwise, and the reaction mixture stirred at room temperature for 69hrs. After this time, the suspended solid was partially in solution but a solid was still observed on the sides of the flask. More phosphorochloridate was added (4.79ml, 2.43mmol), and the reaction mixture stirred for a further 55hrs before being quenched by the addition of sat. NH_4Cl solution (0.25m). After stirring for a further 10mins, the solvent was removed under reduced pressure to give the crude product as a yellow gum which was solubilised in MeOH, dried over $MgSO_4$ (s), filtered and the filtrate reduced to dryness. The residue was solubilised in MeOH, silica added, and then the solvent removed to give the product preabsorbed onto silica which was loaded onto a silica column and eluted with 8% MeOH in $CHCl_3$. The product was further purified by gradient elution from 5→9 MeOH in DCM on a biotage flash-40 column, and after evaporation of the appropriate fractions, the product was obtained as a white foam (70mg, 8.6%).

[0273] The compound had the formula

31P NMR (MeOH- d_4): δ 5.18, 4.86 (1:1).

40 1H NMR: δ 7.67 (1H), 7.37-7.30 (2H), 7.21-7.14 (3H), 6.17-6.10 (1H), 5.97-5.94 (1H), 5.53-5.48 (1H), 4.28-4.15 (2H), 4.00-3.87 (1H), 3.66 (3H), 3.18 (1H), 2.83-2.71 (1H), 1.82-1.66 (1H), 1.36-1.29 (3H).

^{13}C NMR: δ 174.4*, 158.5, 154.1, 151.7, 151.1*, 136.9*, 136.5, 130.7, 129.7, 125.0, 120.4*, 116.8, 68.9*, 59.8, 51.7, 50.5*, 46.0*, 34.2, 19.3*.

MS ES⁺: m/z 488.86 (100%) (M)⁺, 500.04 (12%) (M+Na)⁺, 507.96 (25%) (M+K)⁺.

45 MS FAB: calculated m/z 489.165146, found m/z 489.164677.

In vitro Testing

[0274] Cells were infected with HIV-1 as previously described [Balzarini *et al.* AIDS (1991), 5, 21-28]. Briefly, 5×10^5 cells per milliliter were infected with HIV-1 or HIV-2 at 100 CCID₅₀ (50% cell culture infective dose) per milliliter of cell suspension. Then 100 μL of the infected cell suspension was transferred to microtiter plate wells and mixed with 100 μL of the appropriate dilutions of the test compounds. After 4 days giant cell formation was recorded microscopically in the HIV-infected cell cultures [CEM]. The 50% effective concentration (EC₅₀) and 50% cytotoxic concentration (CC₅₀) were defined as the compound concentrations required to reduce by 50% the number of giant cells or viable cells in the virus-infected and mock-infected cell cultures, respectively.

[0275] In the following Tables data columns are, in order.

HIV1 CEM: EC₅₀ in μM for inhibition of HIV-1 in CEM cells.

EP 1 117 669 B1

HTV1 CEM: EC₅₀ in μM for inhibition of HIV-2 in CEM cells.

CC₅₀ CEM: CC₅₀ in μM for toxicity to CEM cells.

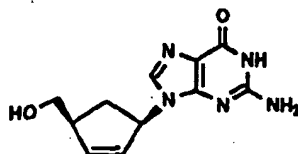
[0276] Table I below contains *in vitro* data comparing the biological activity of compound cf1490 with its non-phosphoramidated counterpart, Abacavir, and with the compound of comparative Example A and its non-phosphoramidated counterpart. Abacavir is currently used in the treatment of patients with HIV infection.

Table I

Compound	EC ₅₀ / μM	EC ₅₀ / μM	CC ₅₀ / μM	Fold Improvement
	HIV-1	HIV-2		
	CEM	CEM	CEM	
1490	0.07	0.09	13.1	30.2
Abacavir	1.9	3	78	
Example A	1.3	0.85	123	1.9
Nonphosphoramidated counterpart of Example A	2	2.3	157	

[0277] As can be seen in Table I compound cf 1490 embodying the present invention shows a much enhanced potency (27 to 33 fold) with respect to HIV *in vitro* than the known non-phosphoramidated Abacavir. The fold improvement in Table I is the mean increase in potency of the phosphoramidate compound versus its parent nucleoside for HIV 1 and HIV 2.

[0278] The surprising nature of this result is demonstrated having regard to Comparative Example A and its non-phosphoramidated counterpart. The structure of the non-phosphoramidated counterpart of Example A is *prima facie* similar to that of Abacavir. The phosphoramidate of Example A, however, shows a potency with respect to HIV which is merely comparable to that of its nonphosphoramidated counterpart, whose structural formula is:



[0279] Table II below compares the *in vitro* potency data of the compound 1490 with known equivalent data disclosed in PCT/GB96/00580 for known phosphoramidated compounds. The data in each case were obtained by the *in vitro* assay described above under "*In vitro* testing"

Table II

Compound	EC ₅₀ / μM	EC ₅₀ / μM	CC ₅₀ / μM
	HTV-1	HIV-2	
	CEM	CEM	CEM
1490	0.07	0.09	13.1
951	0.1	0.07	55
1078	0.55	0.65	209
1093	0.016	0.035	2.57

[0280] Each of compounds 951, 1078 and 1093 is a phosphoramidate of a nucleoside analogue.

[0281] Compound 951 is 2', 3'-dideoxy -2', 3'-didehydrothymidine 5'-(phenyl ethoxycarbonyl) phosphoramidate.

[0282] Compound 1078 is 2', 3'-dideoxy -2', 3'-didehydrothymidine 5'-(phenyl dimethoxyaspartyl) phosphoramidate.

EP 1 117 669 B1

[0283] Compound 1093 is 2', 3'-dideoxy adenosine 5'-(phenyl methoxyalaninyl) phosphoramidate.

[0284] As can be seen from Table II the compound 1490 demonstrates a high degree of potency with respect to HIV.

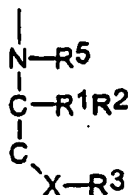
[0285] Potency and toxicity data on an expanded range of compounds is presented in Table III, in which:

5 Cpd and Init refer to the compound reference numbers;

X refers to the aryl (phosphate) moiety;

Y refers to the group;

10



20

Z refers to the bonding in the five membered sugar ring: = is unsaturated pentene;

H is saturated.

25 B in each case is "1592" which refers to the base present in Abacavir.

[0286] The data columns are, in order:

30 HTV 1 CEM: EC₅₀ in μ M for inhibition of HIV1 in CEM cells
HIV2 CEM: EC₅₀ in μ M for inhibition of HIV-2 in CEM cells
HIV2CEM.TK- EC₅₀ μ M for inhibition of HIV-2 in CEM/TK- cells
CC50 CEM: CC₅₀ μ M for toxicity to CEM cells
EC50 MSV: EC₅₀ μ M for inhibition of MSV
35 MCC MSV: minimum cytotoxic concentration in MSV essay.

40

45

50

55

EP 1 117 669 B1

Table III

Ord	Inti	X	Y	Z	B	HV1 CEM	HV2 CEM	HV2 CEM/TC	Q200 CEM	EC200 MSV	MOQ200V
1490	SH	PhO	MeAlaNH	=	1592	0.05	0.05		13.1		1.0 >4
1500	SH	Ol	AlaNH	=	1592	1.2	0.95		11.0		
1502	SH	PhO	BzAlaNH	=	1592	0.093	0.11		12.5		
1503	SH	PhO	Me-D-AlaNH	=	1592	1.38	4.5		64.3		
1504	SH	PhO	Me(Me2Gly)NH	=	1592	0.097	0.08		8.91		
1505	SH	PhO	MePheNH	=	1592	1.42	2.13		36.1		
1507	SH	PhO	EtAlaNH	=	1592	0.07	0.08		12.1		
1508	SH	PhO	MeGlyNH	=	1592	1.78	2		2100		
1509	SH	PhO	Me2AspNH	=	1592	1.42	1.9		44.2		
1510	SH	HO	D-AlaNH	=	1592	1.2	1.2	0.8	213		
1520	SH	p-CIPHO	MeAlaNH	=	1592	0.014	0.063	0.013	4.7		
1540	SH	PhO	IBuAlaNH	=	1592	3.7	8		33	11.7 >20	
1548	SH	PhO	PrAlaNH	=	1592	0.093	0.12		8	2 >4	
1549	SH	PhO	BuAlaNH	=	1592	0.085	0.17		6.23	0.62 >4	
1561	SH	PhO	IPrOAlaNH	=	1592	0.5	0.85		9.18	2.75 >20	
1571	AS	p-MeOCOC(OMe)2CPH	MeAlaNH	=	1592	0.1	0.12		12.1	9.2 >20	
1572	AS	PhO	IPrCH2AlaNH	=	1592	0.09	0.1		14.4	1.98 >4	
1573	AS	PhO	IBuCH2AlaNH	=	1592	0.15	0.18		8.07	2.92 >4	
1574	AS	PhO	IPrCH2CH2AlaNH	=	1592	0.25	0.25		10.7	2.04 >4	
1580	AHA	PhO	MeAlaNH	H	1592	12.5	17.5		237	2100	>100
1585	SS	PhO	3-pentyl Ala NH	=	1592	1.6	2	12.5	19.7	10.1 >20	
1586	SS	PhO	Meval NH	=	1592	3.5	4	3.5	64.1	11.8 >20	
1587	SS	PhO	IBuCH2CH2AlaNH	=	1592	0.2	0.2	0.14	10.2	2.22 >4	
1702	AHA	-	-	H	1592	250	250		178	2100	>100
1706	SH	PhO	nPrAlaNH	=	1592	0.095	0.08		16.4	1.45 >4	
1707	SH	PhO	CH2AlaNH	=	1592	0.33	0.25		10.2	2.84 >4	
1708	SH	PhO	CH2CH2AlaNH	=	1592	0.15	0.18		15.1	1.3 >4	
1709	SH	PhO	Me(CH2CH2Gly)NH	=	1592	1.2	2		18	1.72 >4	
1710	SH	4-Br-PhO	MeAlaNH	=	1592	0.0055	0.049		5.78	0.51 >0.8	
1713	AS	4-MOCC(MeO)2OCH2	MeAlaNH	=	1592	0.053	0.055		14	10.8 >20	
1714	AS	PhO	GLIEASP	=	1592	0.55	2.1		23.1	7.18 >20	
1715	AS	PhO	MeMET	=	1592	1.18	2.73		48.0	10.2 >20	
1716	SS	PhO	MeAlaNH	=	1592	0.55	1.48		22	9.84 >20	
1718	SS	PhO	MeProNH	=	1592	4	5.5		19.4	11.6 >100	
1720	SS	PhO	Br2AspNH	=	1592						
1721	SS	PhO	IPrCH23AlaNH	=	1592	0.05	0.14		12.5	2.2 >4	
1722	SS	PhO	p-PentCH2AlaNH	=	1592	0.13	0.48		18.2		
1737	SH	p-F-PhO	MeAlaNH	=	1592						
1738	SH	p-l-PhO	MeAlaNH	=	1592						
1739	SH	PhO	nPrAlaNH	=	1592						
1740	AS	PhO	Me2GlyNH	=	1592	3.5	5.33		36.9		
1750	AS	PhO	Me2GlyNH	=	1592	3	3.67		18.3		
1751	AS	PhO	MeTpnNH	=	1592	7	5.33		24.2		
1752	AS	PhO	CH2AlaNH	=	1592	1.3	1.05		6.32		

EP 1 117 669 B1

Acid stability

[0287] Compounds were tested for their stability towards acid-mediated hydrolytic decomposition employing a test designed to simulate stomach conditions. Each compound was incubated in dilute HCl of pH1 for 24 hours at 25°C. 0.3mg of compound were added to 1mL of 0.1N HCl at 25°C. HPLC was run immediately for time = 0 and at intervals up to approximately 24 hours.

[0288] The results for compound 1587, and for comparative compounds labelled 1001 and 1093 and described in PCT/GB96/00580, are given in table IV below.

Table IV

Compound	Time (hr)	Compound left (%)
1587	0	100
	22	77
1001	0	0
	17	0
1093	0	100
	13	0

[0289] Compound 1001 disappeared immediately (<1min). Compound 1093 degraded after less than 13 hours. The majority of compound 1587 remained in tact after 22 hours.

[0290] Each of compounds 1001 and 1093 is a phosphoramidate of an adenosine analogue. Compound 1001 is 2', 3' -dideoxy -2',3' dideoxyadenosine-5'-(phenylmethoxyalaninyl) phosphate. Compound 1093 is 2'3' -dideoxy adenosine 5'-(phenyl methoxyalaninyl) phosphate.

[0291] The results given in Table V above demonstrate the acid stability of a compound embodying the present invention compared to known compounds.

Biological stability

[0292] Compound 1587 of the present invention and the two comparative compounds 1001 and 1093 identified above were tested for their stability towards biological decomposition. Each compound was incubated in normal heparinised human plasma at 37°C for 4 hours. At selected time points (0, 15, 30 min, and 1, 2, 4 hours) duplicate samples were removed and deproteinated by acetonitrile extraction. Drug concentrations were then determined by LC/MS/MS analysis using standard methods. The results are shown in Table V below.

Table V

Compound	% Remaining at 4 hours	Half-life (hours)
1587	91	26
1001	52	4.6
1093	50	4.2

[0293] Under the conditions of the test the data in Table V shows a 6-fold stability advantage of compound 1587 over each of compounds 1001 and 1093.

Example 1

(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate Succinate Salt

(a) Phenylethoxy-L-alaninyl phosphorochloridate

[0294] L-alanine ethyl ester hydrochloride (3.0 g, 0.02 moles) was suspended in dry methylene chloride (40 mL). To this suspension was added phenyl phosphorodichloridate (2.9 mL, 0.02 mol) and the mixture was cooled to - 80 °C. N,N-Diisopropylethylamine (Aldrich, 6.8 mL, 0.04 mol) was added to the reaction in aliquots (1-2 mL) over a 1 h time

EP 1 117 669 B1

period. Reaction allowed to warm slowly to room temperature while stirring for 2 h. Organic solvent was removed in vacuo and the residue treated with diethyl ether (100 mL). The diethyl ether solution was filtered to remove insoluble inorganics and concentrated in vacuo to give the product as a colourless syrup. This product was used without further purification in part b.

(b) (1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate

[0295] (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol (1.5 g, 5.2 mmol) was dried by addition of dioxane and concentration in vacuo. To the dried nucleoside was added anhydrous pyridine (10 mL) and tetrahydrofuran (20 mL). Subsequently, tert-butyl magnesium chloride (6 mL, 1M solution in tetrahydrofuran, 6 mmol) was added slowly. The reaction was stirred for 20 min and a solution of phenyl ethoxy-L-alaninyl phosphorochloridate (part a, 3 g, 0.01 mol in 20 mL tetrahydrofuran) was added. The reaction was stirred at room temperature for 10 h and subsequently concentrated in vacuo to a brown syrup. This syrup was dissolved in methylene chloride (100 mL) the methylene chloride extracted with water (2x100 mL), dried (MgSO₄), filtered and concentrated to a brown solid foam. This solid foam was purified by flash chromatography using 5% methanol in chloroform as eluent to give 1.7 g (60 %) of, after purification, a 4:6 mixture of the phosphate isomers as a white solid foam. ¹H-NMR (CDCl₃): δ 7.47 (2 x s, 1H), 7.10-7.46 (m, 5H), 6.07 (m, 1H), 5.9 (m, 1H), 5.78 (s, 1H), 5.5 (m, 1H), 4.84 (bs, 2H), 4.1 (m, 4H), 4.00 (m, 1H), 3.64 (m, 1H), 3.14 (m, 1H), 3.0 (m, 1H), 2.78 (m, 1H), 1.68 (m, 1H), 1.36 (2xd, 3H), 1.22 (2xt, 3H), 0.86 (m, 2H), 0.6 (m, 2H); ³¹P-NMR (CDCl₃): δ 3.05, 3.02.

Anal. Calcd. for C₂₅H₃₂N₇O₅P x 1/4 CHCl₃: C, 53.07; H, 5.70; N, 17.15. Found: C, 52.81; H, 5.95; N, 16.91.

(c) (1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate Succinate Salt

[0296] (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl)phosphate (part 1b, 376 mg, 0.7 mmol) was dissolved in ethanol. To this solution was added succinic acid (82 mg, 0.7 mmol) and the resulting solution evaporated to dryness. The residue was dissolved in acetonitrile (10-20 mL) with heating. Precipitate formed upon cooling. The mixture was stored in the refrigerator overnight and solid collected by filtration to give 330 mg (72 %) of a 4:6 mixture of the phosphate isomers as a solid; ¹H-NMR (DMSO-d₆): δ 12.14 (s, 2H), 7.58 (s, 1H), 7.1-7.4 (m, 6H), 5.9-6.1 (m, 3H), 5.85 (broad s, 2H), 5.42 (m, 1H), 3.95-4.15 (m, 4H), 3.8 (m, 1H), 3.05 (m, 2H), 2.65 (m, 1H), 2.4 (s, 4H), 1.63 (m, 1H), 1.4 (2xd, 3H), 1.12 (t, 3H), 0.5-0.7 (m, 4H); ³¹P-NMR (DMSO-d₆): δ; 4.00 and 3.68; high resolution mass spectrum: calcd for C₂₅H₃₂N₇O₅P (M+H)⁺ (m/z) 542.2281, found 542.2282.

Anal. Calcd. for C₂₅H₃₂N₇O₅P·C₄H₆O₄·1/2H₂O: C, 52.09; H, 5.87; N, 14.66. Found: C, 52.13; H, 5.72; N, 14.61.

Example 2

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate Succinate Salt

(a) Phenylmethoxy-L-alaninyl phosphorochloridate.

[0297] L-alanine methyl ester hydrochloride (10 g, 0.072 mol) was suspended in dry methylene chloride (100 mL). To this suspension was added phenyl phosphorodichloridate (10.7 g, 7.6 mL) and the mixture was cooled to -80 °C. Subsequently N,N-Diisopropylethylamine (Aldrich, 25 mL) was added to the reaction in aliquots (1-2 mL) over a 1 h time period. The solution was stirred for 30 min at -80°C, then allowed to warm slowly to room temperature while stirring for 2 h. Organic solvent was removed in vacuo and the residue treated with diethyl ether (100 mL). The diethyl ether solution was filtered to remove insoluble inorganics and concentrated in vacuo to give the product as a colorless syrup: ³¹P-NMR (CDCl₃) δ 8.61; 8.37 ppm. This product was used without further purification in Example 2b

(b) (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate

[0298] (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol (5.5 g, 0.018 moles) was dried by addition of dioxane and concentration in vacuo. To the dried nucleoside was added anhydrous tetrahydrofuran (30 mL) and pyridine (40 mL). Subsequently tert-butyl magnesium chloride (23 mL, 1M solution in tetrahydrofuran, 1.3 equivalents) was added slowly. The reaction was stirred for 20 min and a solution of phenylmethoxy-L-alaninyl phosphorochloridate (12 g, 0.043 moles, 2.5 equivalents in 20 mL THE) was added. The reaction was stirred

EP 1 117 669 B1

at room temperature for 12 h and subsequently concentrated in vacuo to a brown syrup. This syrup was dissolved in methylene chloride (100 mL) the methylene chloride extracted with water (2x100 mL), dried (MgSO₄), filtered and concentrated to a brown foam. This foam was purified by flash chromatography using 5% methanol in chloroform as eluent to give 6.9 g (75 %) of a mixture of the phosphate isomers of the title compound as a white solid foam. ¹H-NMR (CDCl₃): δ 7.5 (2 x s, 1H), 7.1-7.4 (m, 5H), 6.1 (m, 1H), 5.9 (m, 2H), 5.5-5.6 (m, 1H), 4.9 (bs, 2H), 4.2 (m, 2H), 4.05 (m, 1H), 3.7 (s, 3H), 3.6-3.8 (m, 1H) 3.17 (m, 1H), 3.0 (m, 1H), 2.8 (m, 1H), 1.7 (m, 1H), 1.4 (2 x d, 3H), 0.9 (m, 2H), 0.6 (m, 2H); ³¹P-NMR (CDCl₃): δ 3.07, 3.02.

Anal. Calcd. for C₂₄H₃₀N₇O₅P x 2/5 CHCl₃: C, 50.94; H, 5.33; N, 17.00. Found: C, 50.83; H, 5.39; N, 16.94.

(c) (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate Succinate Salt

[0299] (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate (part b, 100 mg, 0.19 mmol) was dissolved in methanol. To this solution was added succinic acid (22 mg, 0.19 mmol) and the resulting solution evaporated to dryness. The residue was dissolved in acetonitrile (10 mL) with heating. Precipitate formed upon cooling. The mixture was stored in the refrigerator overnight and solid collected by filtration to give 70 mg (57%) of a mixture of the phosphate isomers as a solid; ¹H-NMR (DMSO-d₆): δ 12.15 (s, 2H, D₂O exchangeable), 7.61 (s, 1H), 7.36 (3H, becomes 2H on D₂O exchange), 7.20 (3H), 5.9-6.1 (m, 3H), 5.88 (broad s, 2H, D₂O exchangeable), 5.44 (m, 1H), 4.0-4.2 (m, 2H), 3.85 (m, 1H), 3.60 (s, 3H), 3.05 (2H), 2.65 (m, 1H), 2.44 (s, 4H), 1.64 (m, 1H), 1.23 (m, 3H), 0.5-0.7 (m, 4H); ³¹P-NMR (DMSO-d₆): δ: 3.99 and 3.66;

Anal. Calcd. for C₂₄H₃₀N₇O₅P·C₄H₆O₄·1/2H₂O: C, 51.38; H, 5.70; N, 14.98. Found: C, 51.36; H, 5.66; N, 14.99.

Example 3

(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate Fumarate Salt

[0300] (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl)phosphate (198 mg, 0.37 mmol) was dissolved in ethanol. To this solution was added fumaric acid (43 mg, 0.37 mmol) and the resulting solution evaporated to dryness. The residue was dissolved in acetonitrile (10 mL) with heating. Precipitate formed upon cooling. The mixture was stored in the refrigerator overnight and solid collected by filtration to give 185 mg (75 %) of a 4:6 mixture of the phosphate isomers as a solid; ¹H-NMR (DMSO-d₆): δ 7.6 (s, 1H), 7.1-7.4 (m, 6H), 6.64 (s, 2H), 5.9-6.1 (m, 3H), 5.87 (broad s, 2H), 5.44 (m, 1H), 3.95-4.15 (m, 4H), 3.84 (m, 1H), 3.05 (m, 2H), 2.65 (m, 1H), 1.63 (m, 1H), 1.23 (m, 3H), 1.15 (t, 3H), 0.5-0.7 (m, 4H); ³¹P-NMR (DMSO-d₆): δ: 4.00 and 3.67.

Anal. Calcd. for C₂₅H₃₂N₇O₅P·C₄H₄O₄·1/2H₂O: C, 52.25; H, 5.59; N, 14.71. Found: C, 52.25; H, 5.51; N, 14.49.

Example 4

(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate Glutarate Salt

[0301] (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl)phosphate (part 1b, 200 mg, 0.38 mmol) was dissolved in ethanol. To this solution was added glutaric acid (50 mg, 0.38 mmol) and the resulting solution evaporated to dryness. The residue was dissolved in acetonitrile (10 mL) with heating. The mixture was stored in the refrigerator overnight and solid collected by filtration to give 130 mg (50 %) of a 67:33 mixture of the phosphate isomers as a solid; ¹H-NMR (DMSO-d₆): δ 7.6 (s, 1H), 7.1-7.4 (m, 6H), 5.9-6.1 (m, 3H), 5.87 (broad s, 2H), 5.44 (m, 1H), 3.95-4.2 (m, 4H), 3.8 (m, 1H), 3.1 (m, 2H), 2.65 (m, 1H), 2.25 (t, 4H), 1.7 (m, 3H), 1.23 (m, 3H), 1.15 (t, 3H), 0.5-0.7 (m, 4H); ³¹P-NMR (DMSO-d₆): δ: 4.00 and 3.68.

Anal. Calcd. for C₂₅H₃₂N₇O₅P·C₅H₈O₄·1/2H₂O: C, 52.78; H, 6.05; N, 14.36. Found: C, 52.97; H, 6.07; N, 14.33.

Example 5

(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate D-Tartrate Salt

[0302] (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl)phosphate (157 mg, 0.29 mmol) was dissolved in ethanol. To this solution was added D-tartaric acid (44 mg,

EP 1 117 669 B1

0.29 mmol) and the resulting solution evaporated to dryness. The residue was dissolved in acetonitrile (10 mL) with heating. The mixture was stored in the refrigerator overnight and solid collected by filtration to give 112 mg of a 53:47 mixture of the phosphate isomers as a solid; ¹H-NMR (DMSO-d₆): δ 7.6 (s, 1H), 7.1-7.4 (m, 6H), 5.8-6.2 (m, 5H), 5.44 (m, 1H), 4.3 (s, 2H), 3.95-4.2 (m, 4H), 3.8 (m, 1H), 3.35 (broad s, 2H), 3.1 (m, 2H), 2.65 (m, 1H), 1.7 (m, 1H), 1.23 (m, 3H), 1.15 (t, 3H), 0.5-0.7 (m, 4H); ³¹P-NMR (DMSO-d₆): δ; 4.00 and 3.67.

Example 6

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate Diastereomers

[0303] An approximately 1:1 mixture of diastereomers of (1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate was prepared using similar methodology as above: ¹H-NMR (CDCl₃): δ 7.5 (2 x s, 1H), 7.1-7.4 (m, 5H), 6.1 (m, 1H), 5.9 (m, 2H), 5.5-5.6 (m, 1H), 4.9 (bs, 2H), 4.2 (m, 2H), 4.05 (m, 1H), 3.7 (s, 3H), 3.6-3.8 (m, 1H), 3.17 (m, 1H), 3.0 (m, 1H), 2.8 (m, 1H), 1.7 (m, 1H), 1.4 (2 x d, 3H), 0.9 (m, 2H), 0.6 (m, 2H); ³¹P-NMR (CDCl₃): δ 3.07, 3.02.

Anal. Calcd. for C₂₄H₃₀N₇O₅P x 2/5 CHCl₃: C, 50.94; H, 5.33; N, 17.00. Found: C, 50.83; H, 5.39; N, 16.94.

[0304] The phosphate isomers were separated with Supercritical Fluid Chromatography using a Chiralpak AS (product name) column, 25 % methanol in carbon dioxide as the eluent, flow rate 2 mL/min, temperature 40°C, and pressure 2.068428x10⁷ Pa (3000psi). The first isomer to elute had a RT of 2.9 min and was 100% enantiopure; evaporation of solvents gave the isomer as a white solid foam: ¹H-NMR (CDCl₃): δ 7.50 (s, 1H), 7.3-7.4 (m, 2H), 7.15-7.25 (m, 3H), 6.11 (m, 1H), 5.91 (m, 1H), 5.86 (s, 1H), 5.55 (m, 1H), 4.89 (s, 2H), 4.24 (m, 2H), 4.05 (m, 1H), 3.72 (s, 3H), 3.65 (m, 1H), 3.20 (m, 1H), 3.02 (m, 1H), 2.83 (m, 1H), 1.72 (m, 1H), 1.37 (d, 3H), 0.89 (m, 2H), 0.62 (m, 2H); ³¹P-NMR (CDCl₃): δ 3.07.

Anal. Calcd. for C₂₄H₃₀N₇O₅P x 1/7 CHCl₃: C, 53.25; H, 5.58; N, 18.00. Found: C, 53.27; H, 5.69; N, 17.72.

[0305] The second isomer to elute had a RT of 6.7 min and was 100% enantiopure; evaporation of solvents gave the isomer as a white solid foam: ¹H-NMR (CDCl₃): δ 7.52 (s, 1H), 7.25-7.4 (m, 2H), 7.15-7.22 (m, 3H), 6.11 (m, 1H), 5.94 (m, 1H), 5.85 (s, 1H), 5.55 (m, 1H), 4.88 (s, 2H), 4.22 (m, 2H), 4.04 (m, 1H), 3.75 (s, 3H), 3.7-3.75 (m, 1H), 3.17 (m, 1H), 3.04 (m, 1H), 2.80 (m, 1H), 1.73 (m, 1H), 1.42 (d, 3H), 0.89 (m, 2H), 0.67 (m, 2H); ³¹P-NMR (CDCl₃): δ 3.0.

Anal. Calcd. for C₂₄H₃₀N₇O₅P x 1/5 CHCl₃: C, 52.71; H, 5.52; N, 17.78. Found: C, 52.61; H, 5.67; N, 17.53.

Example 7

(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-methylamino-L-alaninyl) phosphate Sodium Salt

[0306] (1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate (0.060 g, 0.11 mmoles) was suspended in solution of 40% aqueous methylamine (60 ml) and stirred at room temperature for 18 hours. The volatiles were removed by spin evaporation *in vacuo* and the residue was dissolved in water (50 ml), extracted with dichloromethane (2x50 ml) and purified by anion exchange chromatography on a Sep-Pak® Vac 35cc Accell™ Plus QMA cartridge (Waters Corp., P/N WAT054725) (HCO₃⁻ form) with an aqueous ammonium bicarbonate buffer (0 - 0.5 M gradient, 1 L). The appropriate fractions were combined and the volatiles were removed by spin evaporation *in vacuo*. The residue was twice dissolved in deionized water and spin evaporated *in vacuo* to give (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-methylamino-L-alaninyl) phosphate as the ammonium salt. This salt was dissolved in deionized water and passed through a Sep-Pak® Vac 20cc Accell™ Plus CM cartridge (Waters Corp., P/N WAT054675) (Na⁺ form) using deionized water. The appropriate fractions were combined and lyophilized to give 0.026 g (46% yield) of (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-methylamino-L-alaninyl) phosphate sodium salt 2.2 hydrate as a white solid: MS (ES⁻) *m/e* 449 (MH⁻).

Anal. Calcd. for C₁₈H₂₆N₈NaO₄P · 2.2 H₂O: C, 42.22; H, 5.98; N, 21.88. Found: C, 42.36; H, 5.77; N, 21.66.

Example 8

(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-cyclopropylamino-L-alaninyl) phosphate Sodium Salt

[0307] (1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-cyclopropylamino-L-alaninyl) phosphate sodium salt was prepared by a method analogous to that used to prepare (1S,4R)-

EP 1 117 669 B1

4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-methylamino-L-alaninyl) phosphate sodium salt except that the 40% aqueous methylamine solution was replaced by a solution of cyclopropylamine (5 ml, 72 mmoles) in deionized water (50 ml). Lyophilization of the combined fractions gave 35 mg (58% yield) of (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-cyclopropylamino-L-alaninyl) phosphate sodium salt 2.5 hydrate as a white solid: MS (ES⁻) *m/e* 475 (MH⁺).

Anal. Calcd. for C₂₀H₂₈N₈NaO₄P · 2.5 H₂O: C, 44.20; H, 6.12; N, 20.61. Found: C, 44.27; H, 5.81; N, 20.49.

Example 9

(1S,4R)-4-(2-Amino-6-cyclopropylamin-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N,N-dimethylamino-L-alaninyl) phosphate Sodium Salt

[0308] (1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-dimethylamino-L-alaninyl) phosphate sodium salt was prepared by a method analogous to that used to prepare (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-methylamino-L-alaninyl) phosphate sodium salt except that the 40% aqueous methylamine solution was replaced by a 40% aqueous dimethylamine solution (50 ml). Lyophilization of the combined fractions gave 39 mg (59% yield) of (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N,N-dimethylamino-L-alaninyl) phosphate sodium salt trihydrate as a white solid: MS (ES⁻) *m/e* 463 (MH⁺).

Anal. Calcd. for C₁₉H₂₈N₈NaO₄P · 3.0 H₂O: C, 42.22; H, 6.34; N, 20.73. Found: C, 42.40; H, 6.01; N, 20.51

Example 10

(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(L-alaninyl) phosphate Disodium Salt

[0309] (1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate (0.5 g, 0.95 mmoles) was suspended in solution of triethylamine (30 ml) and deionized water (30 ml) and stirred at room temperature for 18 hours. The volatiles were removed by spin evaporation *in vacuo* and the residue was dissolved in water (50 ml), extracted with dichloromethane (2x50 ml) and purified by anion exchange chromatography on a Sep-Pak® Vac 35cc Accell™ Plus QMA cartridge (Waters Corp., P/N WAT054725) (HCO₃⁻ form) with an aqueous ammonium bicarbonate buffer (0 - 0.5 M gradient, 1 L). The appropriate fractions were combined and the volatiles were removed by spin evaporation *in vacuo*. The residue was twice dissolved in deionized water and spin evaporated *in vacuo* to give (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(L-alaninyl) phosphate as the ammonium salt. This salt was dissolved in deionized water and passed through a Sep-Pak® Vac 20cc Accell™ Plus CM cartridge (Waters Corp., P/N WAT054675) (Na⁺ form) using deionized water. The appropriate fractions were combined and lyophilized to give 0.430 g (86% yield) of (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(L-alaninyl) phosphate disodium salt 2.5 hydrate as a white solid: MS (ES⁻) *m/e* 436 (MH⁺).

Anal. Calcd. for C₁₇H₂₂N₇Na₂O₅P · 2.5 H₂O: C, 38.79; H, 5.17; N, 18.63. Found: C, 38.62; H, 5.11; N, 18.43.

Anti-Hepatitis B Virus Activity

[0310] Compounds of Example 1 to 10 were tested for anti-Hepatitis B Virus activity according to the method described by Jansen, R. et al., *Antimicrobial Agents and Chemotherapy*, Vol. 37, No. 3, pp. 441-447, 1993. Representative IC₅₀ values were in the range of 0.017 μM - 3.0 μM.

The solubility and solution/solid state stability of three salt forms of (1S, 4R)-4-[2-amino-6-(cyclopropylamino)-9(H)-purin-9-yl]-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate

[0311] The salts have handling and formulation advantages in that they are stable, free-flowing crystalline solids that do not change composition, even at elevated temperature and humidity. The free base of (1S, 4R)-4-[2-amino-6-(cyclopropylamino)-9(H)-purin-9-yl]-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate in contrast, is a hygroscopic, amorphous solid foam that could not be crystallized.

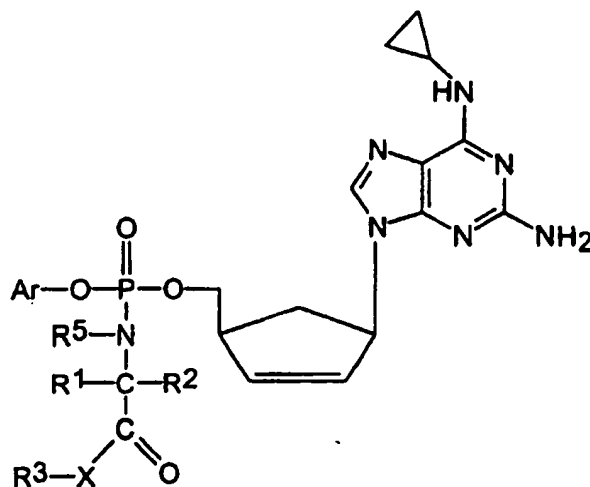
EP 1 117 669 B1

Form	Solid Type*	0.1 N HCl		PBS		HPMC/Tween		Solid State Stability (%)
		Solubility (mg/mL)	Stability (%)	Solubility (mg/mL)	Stability (%)	Solubility (mg/mL)	Stability (%)	
Free Base	Amorphous Hygroscopic	> 5	69.1	0.054	98.5	0.04	97.6	93.7
Glutarate	crystals	>5	69.3	0.084	99.9	>0.25, <1	98.6	98.9
Fumarate	crystals	>5	70.0	0.086	98.5	0.22	98.3	97.1
Succinate	crystals	>5	66.0	0.069	99.8	>0.25, <1	98.8	99.6
Solution stability = % of parent (AUC) after 27 hr at room temperature, normalized to initial AUC.								
Solid state stability = % of parent (AUC) after two weeks at 60°C, normalized to initial AUC.								

[0312] The free bases of the phosphoramidates of 2',3'-dideoxy adenosine and 2',3'-dideoxy-2',3'-didehydroadenosine are hygroscopic amorphous foams or gums. However, their instability to acid prevents advantageous utilization of complexes with acids to form salts with improved physical properties; exposure to acids degrades these compounds rapidly. (1S, 4R)-4-[2-amino-6-(cyclopropylamino)-9(H)-purin-9-yl]-2-cyclopentene-1-methanol (abacavir) has enhanced stability to acid, compared to nucleosides containing labile glycosidic bonds between heterocycle and sugar. Thus phosphoramidate prodrugs of abacavir form stable salts that have been found to have advantageous physical properties suitable for pharmaceutical development.

Claims

1. A compound of the formula (I):



wherein

Ar is an aryl group

R¹ and R² are each independently selected from the group comprising H, alkyl and aryl groups,

X is selected from the group comprising O, NH, NR⁴ and S wherein R⁴ is selected from the group comprising

EP 1 117 669 B1

alkyl and aryl;

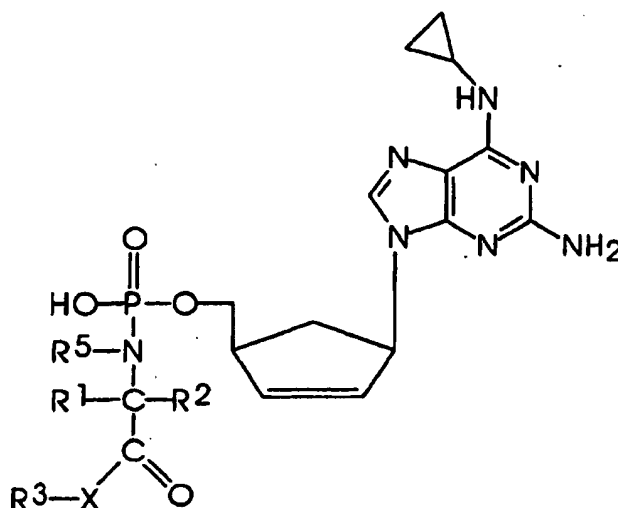
R⁵ is selected from the group comprising H, alkyl and aryl groups, wherein when R¹ and R⁵ are each alkyl they may be linked to form a 5- or 6- membered ring;

and R³ is selected from the group comprising H, alkyl, aryl, heterocyclic and polycyclic groups, or a pharmaceutically acceptable derivative or metabolite thereof.

2. A compound according to claim 1 wherein
Ar is phenyl or substituted phenyl.

3. A compound according to any one of claims 1 to 2 wherein R³ is selected from the group comprising -CH₃, -C₂H₅ and -CH₂Ph.

4. A compound of the formula (II):



wherein R¹, R², R³, R⁵ and X have the meanings ascribed in Claim 1.

5. A compound according to any one of claims 1 to 4 wherein R¹ and R² are the same or different and are H, -CH₃ or -CH₂CH₃.

6. A compound according to any one of claims 1 to 4 wherein R¹ is H and R² is -CH₃, -CH₂CH₃ or -CH₂-Ph.

7. A compound according to any one of claims 1 to 6 wherein the C atom bearing R¹ and R² is chiral.

8. A compound according to any one of claims 1 to 6 wherein the compound has L chirality with respect to the C atom bearing R¹ and R².

9. A compound according to any one of claims 1 to 8 wherein X is O.

10. A compound selected from:

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[L-alaninyl] phosphate diammonium salt

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl benzyloxy-L-

EP 1 117 669 B1

alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-D-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy- α , α -dimethylglycyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-phenylalaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl ethoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxyglycyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl L-aspartyl dimethyl ester] phosphate.

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[4-chlorophenyl methoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl tertbutoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[Phenyl n-propoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[Phenyl n-butoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[Phenyl i-propoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[(p-(2",2"-dimethoxypropionic acid methyl ester) phenyl) methoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl (2-methylpropyl)oxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl (2,2-dimethylpropyl)oxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 3-methylbutoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 3-pentyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-valinyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 3,3-dimethyl-1-butoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[Phenyl n-pentyloxy-L-alaninyl] phosphate

EP 1 117 669 B1

- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[Phenyl cyclohexyloxy-L-alaninyl] phosphate
- 5 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[Phenyl cyclohexanemethoxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[Phenyl methoxy-3-cyclohexane-L-alaninyl] phosphate
- 10 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[4-bromophenyl methoxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl diethoxy-L-aspartyl] phosphate
- 15 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-methionyl] phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-leucinyl]phosphate
- 20 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-prolinyl]phosphate.
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methylene-[phenyl dibenzyloxy-L-aspartinyl]phosphate
- 25 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 4-methyl-1-pentyloxy-L-alaninyl] phosphate
- 30 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl cyclopentylmethoxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[4-fluorophenyl methoxy-L-alaninyl] phosphate
- 35 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[4-iodophenyl methoxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl dimethoxy-L-glutamyl] phosphate
- 40 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-tryptophanyl] phosphate
- 45 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-isoleucinyl] phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl cycloheptan-yloxy-L-alaninyl] phosphate
- 50 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl cyclobutylmethoxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl cyclopropylmethoxy-L-alaninyl] phosphate
- 55 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl cyclobuty-

EP 1 117 669 B1

loxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl cyclopentyl-
loxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl phenethoxy-
L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 3-phenyl-
1-propoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 4-phenyl-
1-butoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 2-cyclohexyl-
1-ethoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 3-cyclohexyl-
1-propoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 4-cyclohexyl-
1-butoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy- α -
ethyl-L-glyciny] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy- α -
phenyl(RS)glyciny] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy- α -
propyl-L-glyciny] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-([phenyl methoxy- α -
butyl-RS-glyciny])phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-phenoxyphenyl
methoxy-L-alaninyl]phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-phenylphenyl
methoxy-L-alaninyl])phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[4-hydroxyacetophe-
none methoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[4-butylphenyl meth-
oxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-methoxyphenyl
methoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-propoxyphenyl
methoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy- α ,
 α -cyclopentylglyciny] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy- α ,
 α -cylohexylglyciny] phosphate

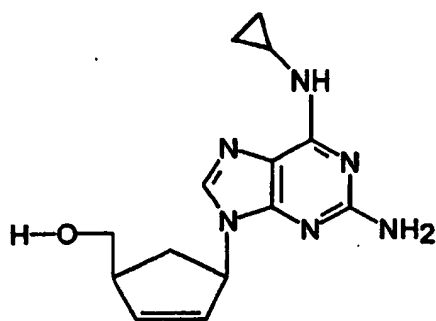
EP 1 117 669 B1

- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy- α ,
 α -cylopropylglycyl] phosphate
- 5 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-(methoxycarbo-
 nyl)phenyl methoxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-(trifluoromethylthio)phenyl methoxy-L-alaninyl] phosphate
- 10 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-(2-methoxyvinyl)
 phenyl methoxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-(2-phenylcarbonyl-
 vinyl)phenyl methoxy-L-alaninyl] phosphate
- 15 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-(2,2-dicyanovinyl)
 phenyl methoxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[o-(carboxylate ethyl
 ester)phenyl methoxy-L-alaninyl] phosphate
- 20 (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-
 alaninyl) phosphate succinate salt
- 25 (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-
 alaninyl) phosphate succinate salt
- (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-
 alaninyl) phosphate fumarate salt
- 30 (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-
 alaninyl) phosphate glutarate salt
- (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-
 alaninyl) phosphate D-tartrate salt
- 35 (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-
 alaninyl) phosphate diastereoisomers
- 40 (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-methyl-
 amino-L-alaninyl) phosphate sodium salt
- (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-cyclopro-
 pylamino-L-alaninyl) phosphate sodium salt
- 45 (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N,N-dimeth-
 ylamino-L-alaninyl) phosphate sodium salt
- 50 (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(L-alaninyl) phos-
 phate disodium salt.

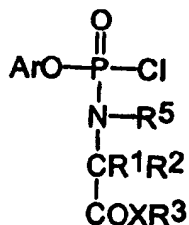
11. Use of a compound according to any one of claims 1 to 3, to claim 10, or to any one of claims 5 to 9 as dependent
 on any one of claims 1 to 3 in the manufacture of a medicament for the treatment or prophylaxis of a viral infection.
- 55 12. Use of a compound according to claim 11 wherein the viral infection comprises HIV.
13. Use of a compound according to claim 11 wherein the viral infection comprises HBV.

EP 1 117 669 B1

14. A compound according to any one of claims 1 to 3, to claim 10, or to any one of claims 5 to 9 as dependent on any one of claims 1 to 3 for use in a method of treatment, prophylaxis or diagnosis.
15. A compound according to claim 14 wherein the method comprises a method of prophylaxis or treatment of viral infection comprising administration to a patient in need of such treatment an effective dose of the compound.
16. A compound according to claim 15 wherein the viral infection is HIV.
17. A compound according to claim 15 wherein the viral infection is HBV.
18. A compound according to any one of claims 14 to 17 wherein the method comprises administering orally to a patient an effective dose of the compound.
19. A pharmaceutical composition comprising a compound according to any one of claims 1 to 3, to claim 10, or to any one of claims 5 to 9 as dependent on any one of claims 1 to 3 in combination with a pharmaceutically acceptable excipient.
20. A composition according to claim 19 in a form for oral administration.
21. A process for the preparation of a compound according to any one of claims 1 to 3, to claim 10, or to any one of claims 5 to 9 as dependent on any one of claims 1 to 3 comprising reacting a compound having the formula



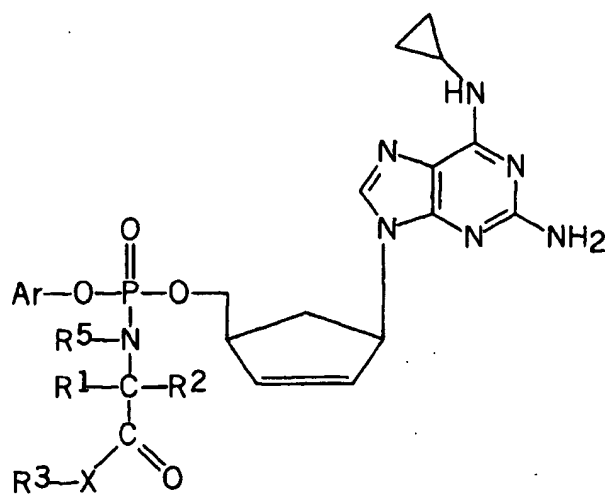
with a compound of formula



Revendications

1. Un composé de formule (I):

EP 1 117 669 B1



où

Ar est un groupement aryle

R¹ et R² sont chacun sélectionnés indépendamment parmi le groupe composé de H, de groupements alkyle et aryle,

X est sélectionné à partir du groupe composé de O, NH, NR⁴ et S où R⁴ est sélectionné parmi le groupe comprenant les alkyle et aryle ;

R⁵ est sélectionné parmi le groupe composé de H, de groupements alkyle et aryle, où lorsque R¹ et R⁵ sont chacun alkyle ils peuvent être reliés pour former un noyau à 5 ou 6 membres ;

et R³ est sélectionné parmi le groupe comprenant les H, groupements alkyle et aryle hétérocycliques et polycycliques,

ou un dérivé ou métabolite pharmaceutiquement acceptable de celui-ci.

2. Un composé suivant la revendication 1 où

Ar est le phényle ou phényle substitué.

3. Un composé suivant n'importe laquelle des revendications 1 à 2 où R³ est sélectionné parmi le groupe comprenant les -CH₃, -C₂H₅ et -CH₂Ph.

4. Un composé de formule (II):

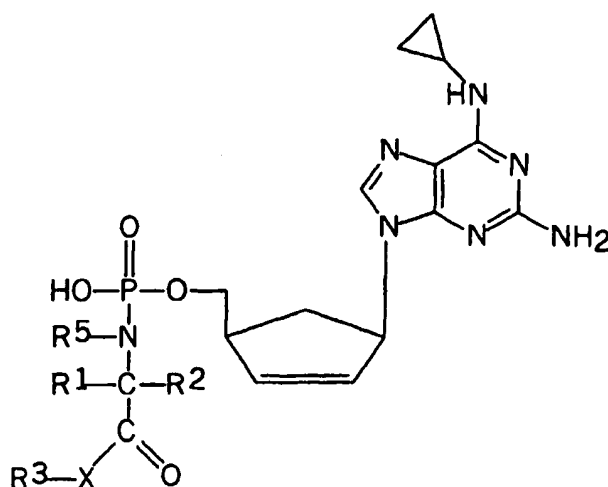
EP 1 117 669 B1

5

10

15

20



où R¹, R², R³, R⁵ et X ont les significations décrites dans la Revendication 1.

25 5. Un composé suivant n'importe laquelle des revendications 1 à 4 où R¹ et R² sont identiques ou différents et sont H, -CH₃ ou -CH₂CH₃.

6. Un composé suivant n'importe laquelle des revendications 1 à 4 où R¹ est H et R² est -CH₃, -CH₂CH₃ ou -CH₂-Ph.

30 7. Un composé suivant n'importe laquelle des revendications 1 à 6 où l'atome C qui contient R¹ et R² est chiral.

8. Un composé suivant n'importe laquelle des revendications 1 à 6 où le composé a une chiralité L par rapport à l'atome C qui contient R¹ et R².

35 9. Un composé suivant n'importe laquelle des revendications 1 à 8 où X est O.

10. Un composé sélectionné parmi :

40 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-L-alaninyl] phosphate.

Sei de (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[L-alaninyl] phosphate diammonium.

45 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl benzyloxy-L-alaninyl] phosphate.

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-D-alaninyl] phosphate.

50

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-α,α-diméthylglyciny] phosphate.

55

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-L-phénylalaninyl] phosphate.

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl éthoxy-L-alaninyl] phosphate.

EP 1 117 669 B1

- (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxyglycyl] phosphate.
- 5 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl L-aspartyl diméthyle ester] phosphate.
- (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[4-chlorophényl méthoxy-L-alaninyl] phosphate.
- 10 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl tertbutyloxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[Phényl n-propoxy-L-alaninyl] phosphate
- 15 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[Phényl n-butyloxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[Phényl i-propoxy-L-alaninyl] phosphate
- 20 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[(p-(2",2"-acide diméthoxypropionique méthyl ester) phényl) méthoxy-L-alaninyl] phosphate
- 25 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl (2-méthylpropyl)oxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl (2,2-diméthylpropyl)oxy-L-alaninyl] phosphate
- 30 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl 3-méthylbutyloxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl 3-pentyloxy-L-alaninyl] phosphate
- 35 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-L-valinyl] phosphate
- 40 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl 3,3-diméthyl-1-butyloxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[Phényl n-pentyloxy-L-alaninyl] phosphate
- 45 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[Phényl cyclohexyloxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[Phényl cyclohexaneméthoxy-L-alaninyl] phosphate
- 50 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[Phényl méthoxy-3-cyclohexane-L-alaninyl] phosphate
- 55 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[4-bromophényl méthoxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl diéthoxy-L-as-

EP 1 117 669 B1

partyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-L-méthionyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-L-leuciny] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-L-prolinyl] phosphate.

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl dibenzoyloxy-L-aspartinyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl 4-méthyle-1-pentyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amio-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl cyclopentylméthoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[4-fluorophényl méthoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[4-iodophényl méthoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl diméthoxy-L-glutamyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-L-tryptophanyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-L-isoleucinyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl cycloheptanyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl cyclobutylméthoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl cyclopropylméthoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl cyclobutyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl cyclopentylloxy-L-alaninyl]phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl phénéthoxy-L-alaninyl]phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl 3-phényl-1-propoxy-L-alaninyl]phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl 4-phényl-1-butoxy-L-alaninyl] phosphate

EP 1 117 669 B1

- (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl 2-cyclohexyl-1-éthoxy-L-alaninyl] phosphate
- 5 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl 3-cyclohexyl-1-propoxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl 4-cyclohexyl-1-butoxy-L-alaninyl] phosphate
- 10 (1S,4R)-4-[2-amio-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-a-éthyl-L-glyciny] phosphate
- (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-a-phényl(RS)glyciny] phosphate
- 15 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-a-propyl-L-glyciny] phosphate
- (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-([phényl méthoxy-a-butyl-RS-glyciny] phosphate
- 20 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[p-phénoxyphényl méthoxy-L-alaninyl]phosphate
- (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[p-phénylphényl méthoxy-L-alaninyl]phosphate
- 25 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanoD-[4-hydroxyacetophénone méthoxy-L-alaninyl] phosphate
- 30 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[4-butylphényl méthoxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[p-méthoxyphényl méthoxy-L-alaninyl] phosphate
- 35 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[p-propoxyphényl méthoxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy- α,α -cyclopentylglyciny] phosphate
- 40 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy- α,α -cylohexylglyciny] phosphate
- 45 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-a,a-cylopropylglyciny] phosphate
- (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol 1 O-[p-(méthoxycarbonyl)phényl méthoxy-L-alaninyl] phosphate
- 50 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[p-(trifluorométhylthio)phényl méthoxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[p-(2-méthoxyvinyl)phényl méthoxy-L-alaninyl] phosphate
- 55 (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanoD-[p-(2-phénylcarbonylvi-

EP 1 117 669 B1

- nyl)phényl méthoxy-L-alaninyl] phosphate
- (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[p-(2,2-dicyanovinyl)phényl méthoxy-L-alaninyl] phosphate
- 5 (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[o-(carboxylate éthyl ester)phényl méthoxy-L-alaninyl] phosphate
- 10 Sel succinate de (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentène-1-méthanol O-(phényl éthoxy-L-alaninyl) phosphate
- Sel succinate de (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentène-1-méthanol O-(phényl méthoxy-L-alaninyl) phosphate
- 15 Sel fumarate de (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentène-1-méthanol O-(phényl éthoxy-L-alaninyl) phosphate
- Sel glutarate de (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentène-1-méthanol O-(phényl éthoxy-L-alaninyl) phosphate
- 20 Sel D-tartrate de (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentène-1-méthanol O-(phényl éthoxy-L-alaninyl) phosphate
- Diastéréoisomères de (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentène-1-méthanol O-(phényl méthoxy-L-alaninyl) phosphate
- 25 Sel de (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentène-1-méthanol O-(phényl N-méthylamino-L-alaninyl) phosphate sodique
- 30 Sel de (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentène-1-méthanol O-(phényl N-cyclopropylamino-L-alaninyl) phosphate sodique
- Sel de (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentène-1-méthanol O-(phényl N,N-diméthylamino-L-alaninyl) phosphate sodique
- 35 Sel de (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentène-1-méthanol O-(L-alaninyl) phosphate disodique
- 40 11. L'utilisation d'un composé suivant n'importe laquelle des revendications 1 à 3, la revendication 10 ou n'importe laquelle des revendications 5 à 9 comme il dépend de n'importe laquelle des revendications 1 à 3 dans la fabrication d'un médicament pour le traitement ou la prophylaxie d'une infection virale.
12. L'utilisation d'un composé suivant la revendication 11 où l'infection virale comprend le VIH.
- 45 13. L'utilisation d'un composé suivant la revendication 11 où l'infection virale comprend le VHB.
14. Un composé suivant n'importe laquelle des revendications 1 à 3, la revendication 10 ou n'importe laquelle des revendications 5 à 9 comme il dépend de n'importe laquelle des revendications 1 à 3 destiné à l'usage dans une méthode de traitement, de prophylaxie ou de diagnostic.
- 50 15. Un composé suivant la revendication 14 où la méthode comprend une méthode de prophylaxie ou de traitement d'une infection virale comprenant l'administration à un patient qui a besoin de ce traitement d'une dose efficace du composé.
- 55 16. Un composé suivant la revendication 15 où l'infection virale est le VIH.
17. Un composé suivant la revendication 15 où l'infection virale est le VHB.

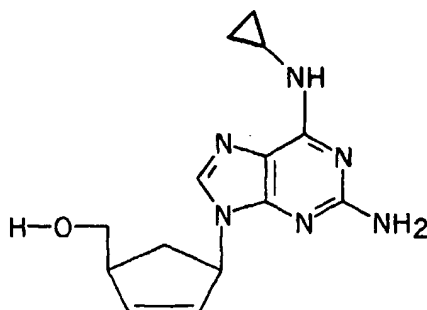
EP 1 117 669 B1

18. Un composé suivant n'importe laquelle des revendications 14 à 17 où la méthode comprend l'administration par voie orale à un patient d'une dose efficace de composé.

19. Une composition pharmaceutique comprenant un composé suivant n'importe laquelle des revendications 1 à 3, la revendication 10 ou n'importe laquelle des revendications 5 à 9 comme il dépend de n'importe laquelle des revendications 1 à 3 en association avec un excipient pharmaceutiquement acceptable.

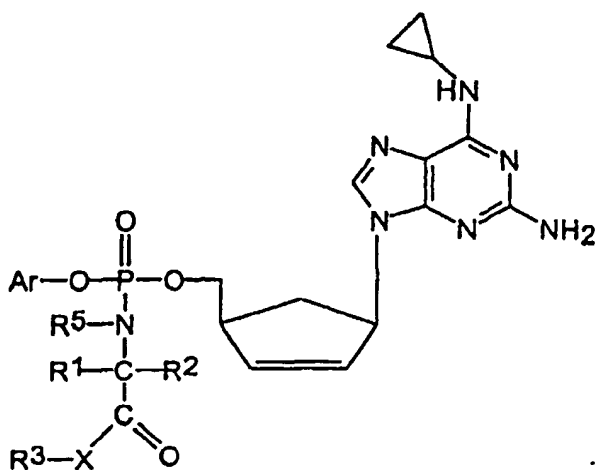
20. Une composition suivant la revendication 19 sous une forme destinée à la voie orale.

21. Un procédé pour la préparation d'un composé suivant n'importe laquelle des revendications 1 à 3, la revendication 10 ou n'importe laquelle des revendications 5 à 9 comme il dépend de n'importe laquelle des revendications 1 à 3 qui comprend la mise en réaction d'un composé qui a pour formule



Patentansprüche

1. Verbindung der Formel (I):



in der

Ar eine Arylgruppe ist;

R¹ und R² jeweils unabhängig aus der Gruppe gewählt werden, die H, Alkyl und Arylgruppen umfasst;

EP 1 117 669 B1

X aus der Gruppe gewählt ist, die O, NH, NR⁴ und S umfaßt, wobei R⁴ aus der Gruppe gewählt ist, die Alkyl und Aryl umfaßt;

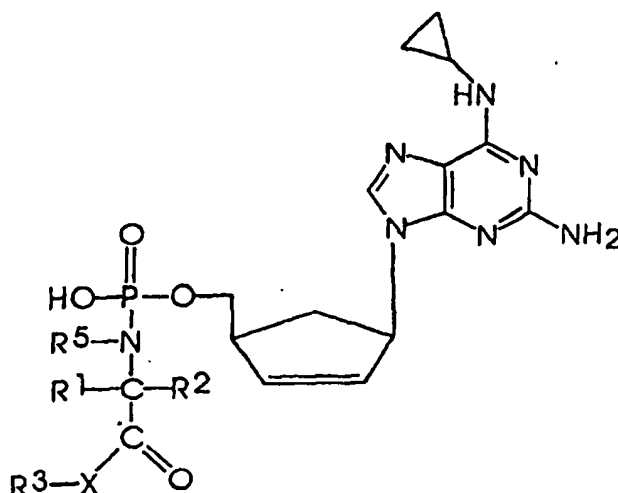
R⁵ aus der Gruppe gewählt ist, die H, Alkyl- und Arylgruppen umfaßt, wobei, wenn R¹ und R⁵ jeweils Alkyl sind, sie unter Bildung eines 5- oder 6-gliedrigen Ringes verknüpft sein können;

und R³ aus der Gruppe gewählt ist, die H, Alkyl-, Aryl-, heterocyclische und polycyclische Gruppen umfaßt; oder ein pharmazeutisch annehmbares Derivat oder Metabolit davon.

2. Verbindung gemäß Anspruch 1, wobei Ar Phenyl oder substituiertes Phenyl ist.

3. Verbindung gemäß einem der Ansprüche 1 bis 2, wobei R³ aus der Gruppe gewählt ist, die -CH₃, -C₂H₅ und -CH₂Ph umfaßt.

4. Verbindung der Formel (II):



in der R¹, R², R³, R⁵ und X die in Anspruch 1 zugewiesenen Bedeutungen besitzen.

5. Verbindung gemäß einem der Ansprüche 1 bis 4, in der R¹ und R² gleich oder unterschiedlich sind und H, -CH₃ oder -CH₂CH₃ sind.

6. Verbindung gemäß einem der Ansprüche 1 bis 4, in der R¹ H ist und R² -CH₃, -CH₂CH₃ oder -CH₂-Ph ist.

7. Verbindung gemäß einem der Ansprüche 1 bis 6, in der das C-Atom, welches R¹ und R² trägt, chiral ist.

8. Verbindung gemäß einem der Ansprüche 1 bis 6, in der die Verbindung L-Chiralität in Bezug auf das C-Atom, welches R¹ und R² trägt, besitzt.

9. Verbindung gemäß einem der Ansprüche 1 bis 8, in der X O ist.

10. Verbindung, gewählt aus:

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[L-alaninyl]phosphat-diammoniumsalz

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylbenzyloxy-L-alaninyl]phosphat

EP 1 117 669 B1

- (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-D-alaninyl]phosphat
- 5 (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy- α,α -dimethylglycinyl]phosphat
- (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-L-phenylalaninyl]phosphat
- 10 (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylethoxy-L-alaninyl]phosphat
- (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxyglycinyl]phosphat
- 15 (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-L-aspartyl(methylester)]phosphat
- (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[4-chlorophenylmethoxy-L-alaninyl]phosphat
- 20 (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyltertbutyloxy-L-alaninyl]phosphat
- (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-n-propoxy-L-alaninyl]phosphat
- 25 (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-n-butyloxy-L-alaninyl]phosphat
- 30 (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-i-propoxy-L-alaninyl]phosphat
- (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[(p-(2",2"-dimethoxypropionsäuremethylester)phenyl)methoxy-L-alaninyl]phosphat
- 35 (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl(2-methylpropyl)oxy-L-alaninyl]phosphat
- (1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-(2,2-dimethylpropyl)oxy-L-alaninyl]phosphat
- 40 (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-3-methylbutyloxy-L-alaninyl]phosphat
- 45 (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-3-pentyloxy-L-alaninyl]phosphat
- (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-L-valinyl] phosphat
- 50 (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-3,3-dimethyl-1-butyloxy-L-alaninyl]phosphat
- (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-n-pentyloxy-L-alaninyl]phosphat
- 55 (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylcyclohexylo-

EP 1 117 669 B1

xy-L-alaninyl]phosphat

(1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylcyclohexanmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-3-cyclohexan-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[4-bromophenylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyldiethoxy-L-aspartyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-L-methionyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-L-leuciny]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-L-prolinyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methylen-[phenyldibenzoyloxy-L-aspartinyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-4-methyl-1-pentyloxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylcyclopentylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[4-fluorophenylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[4-iodophenylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyldimethoxy-L-glutamyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-L-tryptophanyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-L-isoleucinyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-Methanol-O-[phenylcycloheptanyloxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-Methanol-O-[phenylcyclobutylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-Methanol-O-[phenylcyclopropylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-Methanol-O-[phenylcyclobutyloxy-L-alaninyl]phosphat

EP 1 117 669 B1

- (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylcyclopentyl-
oxy-L-alaninyl]phosphat
- 5 (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylphenethoxy-
L-alaninyl]phosphat
- (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-3-phenyl-
1-propoxy-L-alaninyl]phosphat
- 10 (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-4-phenyl-
1-butoxy-L-alaninyl]phosphat
- (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-2-cyclohexyl-
1-ethoxy-L-alaninyl]phosphat
- 15 (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-3-cyclohexyl-
1-propoxy-L-alaninyl]phosphat
- (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-4-cyclohexyl-
1-butoxy-L-alaninyl]phosphat
- 20 (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy- α -
ethyl-L-glycinyl]phosphat
- 25 (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy- α -
phenyl(RS)glycinyl]phosphat
- (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy- α -
propyl-L-glycinyl]phosphat
- 30 (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy- α -
butyl-RS-glycinyl]phosphat
- (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[p-phenoxyphenyl-
methoxy-L-alaninyl]phosphat
- 35 (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[p-phenylphenyl me-
thoxy-L-alaninyl]phosphat
- (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[4-hydroxyacetophe-
nonmethoxy-L-alaninyl]phosphat
- 40 (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[4-butylphenylme-
thoxy-L-alaninyl]phosphat
- 45 (1 S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[p-methoxyphenyl-
methoxy-L-alaninyl]phosphat
- (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[p-propoxyphenylme-
thoxy-L-alaninyl]phosphat
- 50 (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy- α , α -
cyclopentylglycinyl]phosphat
- 55 (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy- α , α -
cyclohexylglycinyl]phosphat
- (1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy- α , α -

EP 1 117 669 B1

cylopropylglyciny]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[p-(methoxycarbonyl)phenylmethoxy-L-alaniny]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[p-(trifluormethylthio)phenylmethoxy-L-alaniny]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[p-(2-methoxyvinyl)phenylmethoxy-L-alaniny]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[p-(2-phenylcarbonylvinyl)phenylmethoxy-L-alaniny]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[p-(2,2-dicyanovinyl)phenylmethoxy-L-alaniny]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[o-(carboxylatethylester)phenylmethoxy-L-alaniny]phosphat

(1S, 4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopenten-1-methanol-O-(phenylethoxy-L-alaniny]phosphat-succinatsalz

(1S, 4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopenten-1-methanol-O-(phenylmethoxy-L-alaniny]-phosphat-succinatsalz

(1S, 4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopenten-1-methanol-O-(phenylethoxy-L-alaniny]phosphat-fumaratsalz

(1S, 4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopenten-1-methanol-O-(phenylethoxy-L-alaniny]phosphat-glutaratsalz

(1S, 4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopenten-1-methanol-O-(phenylethoxy-L-alaniny]phosphat-D-tartratsalz

(1S, 4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopenten-1-methanol-O-(phenylmethoxy-L-alaniny]phosphatdiastereoisomere

(1S, 4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopenten-1-methanol-O-(phenyl-N-methylamino-L-alaniny]phosphat-natriumsalz

(1S, 4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopenten-1-methanol-O-(phenyl-N-cyclopropylamino-L-alaniny]phosphat-natriumsalz

(1S, 4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopenten-1-methanol-O-(phenyl-N,N-dimethylamino-L-alaniny]phosphat-natriumsalz

(1S, 4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopenten-1-methanol-O-(L-alaniny]phosphat-dinatriumsalz

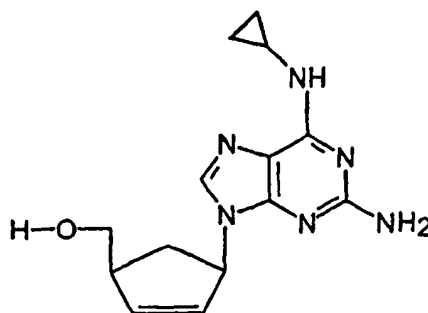
11. Verwendung einer Verbindung gemäß einem der Ansprüche 1 bis 3, gemäß Anspruch 10 oder gemäß einem der Ansprüche 5 bis 9, welche von einem der Ansprüche 1 bis 3 abhängen, bei der Herstellung eines Medikamentes zur Behandlung oder Prophylaxe einer viralen Infektion.

12. Verwendung einer Verbindung gemäß Anspruch 11, bei der die virale Infektion HIV umfaßt.

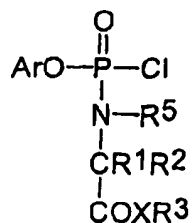
13. Verwendung einer Verbindung gemäß Anspruch 11, bei der die virale Infektion HBV umfaßt.

EP 1 117 669 B1

14. Verbindung gemäß einem der Ansprüche 1 bis 3, gemäß Anspruch 10 oder gemäß einem der Ansprüche 5 bis 9, welche von einem der Ansprüche 1 bis 3 abhängen, zur Verwendung bei einem Verfahren zur Behandlung, Prophylaxe oder Diagnose.
15. Verbindung gemäß Anspruch 14, bei der das Verfahren ein Verfahren der Prophylaxe oder Behandlung einer viralen Infektion umfaßt, umfassend das Verabreichen einer wirksamen Dosis der Verbindung an einen eine solche Behandlung benötigenden Patienten.
16. Verbindung gemäß Anspruch 15, wobei die virale Infektion HIV ist.
17. Verbindung gemäß Anspruch 15, wobei die virale Infektion HBV ist.
18. Verbindung gemäß mindestens einem der Ansprüche 14 bis 17, wobei das Verfahren das orale Verabreichen einer wirksamen Dosis der Verbindung an einen Patienten umfaßt.
19. Pharmazeutische Zusammensetzung, umfassend eine Verbindung gemäß einem der Ansprüche 1 bis 3, gemäß Anspruch 10 oder gemäß einem der Ansprüche 5 bis 9, welche von einem der Ansprüche 1 bis 3 abhängen, in Kombination mit einem pharmazeutisch annehmbaren Vehikel.
20. Zusammensetzung gemäß Anspruch 19 in einer Form zur oralen Verabreichung.
21. Verfahren zur Herstellung einer Verbindung gemäß einem der Ansprüche 1 bis 3, gemäß Anspruch 10 oder gemäß einem der Ansprüche 5 bis 9, welche von einem der Ansprüche 1 bis 3 abhängen, umfassend das Umsetzen einer Verbindung der Formel



mit einer Verbindung der Formel



**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☒ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.